GLOMERULAR NEPHRITIS

DIAGNOSIS AND TREATMENT



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Microdissection of a lobule from a normal, adult kidney. About the periphery of the lobule lie the glomeruli, each surrounded by the periglomerular mass of its proximal convolution and associated distal convolution. From this cluster two tubules pass to and from the central medullary ray, the terminal portion of the proximal convolution entering, the ascending limb of Henle's loop departing. In the sheaf of straight tubules that compose the ray, the junction of the collecting tubules can be occasionally seen (× 15)

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THOMAS ADDIS, M.D., F.R.C.P., (Edin.)

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Dedicated to the patients, laboratory workers, dietitians, medical students, and doctors who have worked in the Nephritis Clinic of the Out-patient Department of Stanford University Medical School in San Francisco. Here they will find a record of their observations and of the conversations and controversies in which they have taken part over many years.

Affectus qui passio est, desinit esse passio, simulatque eius, claram et distinctam formamus ideam.

Spinoza, *Ethics*, part V, prop. 3.

INTRODUCTION

This book is written because we have come to the conclusion that the present-day treatment of patients with renal disease is inadequate and sometimes dangerous. There is no universally accepted plan of treatment, but none of the current proposals takes cognizance of the therapeutic efficacy of rest. In the past the giving of rest to the diseased kidney was explicitly recognized as the theoretical justification for various dietary prohibitions and as the reason for the administration of drugs that induced sweating and purging. But in those days we did not know how the kidney worked, and so we did not know how to give it rest. Today, though we know something about the work of the kidney, we find the principle of rest implicitly, if not explicitly, denied. Recognizing the errors in the dietetic treatment of the past, and influenced by accumulating evidence as to the deleterious effects of protein undernutrition, the leaders of investigation in this field treat patients with renal disease, particularly those with edema, in such a way as to impose an unnecessary amount of work on the kidneys. On theoretical, experimental, and clinical grounds we have slowly reached the conclusion that this is a dangerous error. This whole book may be taken as a reasoned exposition of that view.

In general, then, our subject is the theory of the application of this principle of rest in the case of any patient in whom any disease has led to a substantial reduction in the number of functioning nephrons. But whenever we try to apply the theory in practice we find we cannot use it effectively for any individual patient until we know him and his situation and have learned from direct, clinical observation of his blood and urine as much as we can about the nature and the extent of his renal lesion. This information modifies and controls the endeavor to contrive those conditions, consistent with adequate nutrition, under which the minimum amount of renal osmotic work will be imposed. Without this knowledge the application of the principle is only formal and schematic and, in detail, very likely ill-advised. So the general theory can be converted from an abstraction into a reality only insofar as it is fitted in detail to the specific conditions that exist in particular diseases and in particular patients suffering from these diseases. This task we cannot undertake. There is only one disease of the kidneys in which we have had an experience sufficiently extensive, detailed, and prolonged to

application of the theory of rest from osmotic work may be illustrated. This disease is glomerular nephritis. The title of the book is, therefore, *Glomerular Nephritis: Diagnosis and Treatment.*

The methods we use in our clinical work can be used in any doctor's office. We believe this, because, like most doctors who are not specialists, we have to make our own clinical observations. We have no chemists working for us, and, in any case, most of our patients are not able to pay for repeated determinations of urea, creatinine, and protein in their blood serum or for frequent estimates of the rate of protein excretion in their urine. When we came to see that rational treatment required the reiteration of these and other measurements over long periods of time, we were thus confronted with the necessity of doing the work ourselves. But we had no time to take histories, make physical examinations, and treat our patients, and also to determine the quantity of these materials by means of the standard laboratory methods. We were forced to contrive a series of extremely rapid methods, so simple and mechanical in their operation that the possibility of large error is excluded, and so direct that the results are presented as pictures whose significance can be read at a glance.

It may seem that methods of admittedly only approximate accuracy are to be justified, if at all, as merely makeshift contrivances, to be used when no laboratory facilities are available or when the economic status of the patient makes it impossible to obtain the services of those who can give us more precise results This perfectly natural view is based, however, on a misapprehension as to the purpose of these methods. These are clinical, not laboratory, methods. They are designed to make the examination of the blood and urine a part of the physical examination of the patient. The results they give sometimes raise questions that can be answered only by the use of laboratory methods for which the doctor has no time. But they cannot be replaced by any laboratory method, no matter how precise and elaborate. They give us, while we are still working with the patient, information that is useful for any patient and indispensable for those with renal disease.

We are well aware that this enthusiasm for laboratory methods so quick and simple that they merge with inspection, palpation, percussion, and auscultation will amuse many of our most experienced readers. This is what they have always wanted, often tried for, and always failed to get. Their skepticism is founded on hope repeatedly denied. They know very well that a good doctor will not leave his patient for any physical or chemical manipulation, no matter how easy it may be. We know that too, and we are not supposing that the doctor will ever measure and

centrifuge blood and urine. All that is required is that he will give them a glance after they have been manipulated, and see them as part of the patient—as much a part of him as his build and manner, the appearance of his retina, or the size and shape of the shadow of his heart. Even so, there will still be doubt because someone has to do the work. If the doctor cannot do it, who will? The problem has not been solved; it has only been transformed into a problem of organization that may be equally insoluble.

Our experience, however, shows that in this new form there is no longer any material difficulty. Since no nurses are assigned to our clinic, we asked for help from patients and friends. They were neither biochemists nor dietitians, but ordinary people who liked to work in a group of ordinary people to help other ordinary people. By contributing their ideas as well as their work they have helped us all to develop the laboratory and dietetic methods we describe to their present level of simplicity and reliability. It is true, of course, that the conditions in our out-patient clinic are in some respects quite different from those that exist in most doctors' offices, and that in some places it may be difficult to get such help as we received. But nowadays the fact that a doctor needs assistance if he is to work with efficiency and celerity is recognized in practice, so that almost every doctor has an office nurse who works with him in all sorts of ways What we propose is that the office nurse be asked to undertake this most important and interesting work which already goes far beyond patients with renal disease and, in principle, can be extended to cover the examination of every patient. This would be the simplest possible clinical team—the patient, the doctor, and the office nurse. This book may be regarded as an introductory handbook for just such a group.

A reader familiar with the world literature on nephritis may be disappointed to find that no attempt has been made to connect our observations with those made by clinical investigators elsewhere. We can only ask him to remember that we are not trying to harvest all that is of value in this field. We are trying to say something new about out-patient and office practice. This is an enterprise so difficult and dangerous that we cannot afford to go far beyond what we ourselves have seen and know. Thus we make no references to any clinical facts that cannot readily be demonstrated in any doctor's office. This is a severe limitation, for though office work is admirably adapted for obtaining a broad survey of the development of disease over long periods of time, we cannot hope, with our simple methods, to explore deeply the status of any one patient at any one time or expect to be able to analyze in detail the interplay of the factors responsible for his immediate symptoms. That is the task of

the clinical investigator working with the patient when he is in bed and in a hospital. Office work has a quality that may be described as extensive. It can never hope to be intensive. So two books should be written about the treatment of glomerular nephritis—one embodying the experience of the practical doctor, the other the experience of the hospital physician. Both have their place and their use, but neither alone can encompass all that should be said on this subject; neither can present the problem as it really exists, in depth as well as in breadth. In spite of this limitation in our experience it may be hoped that some of the deeper understanding that is coming to us through investigations on patients in the hospital does pervade the text as an unacknowledged background for much that is said And insofar as there is anything novel in what we say, a good deal of the confidence with which our views are presented derives from the feeling that they are only an inevitable development of what has already been said by others. We hope that it will thus become apparent to the scholarly reader that at every step we have been guided and supported by the work of our colleagues.

This, however, is not a textbook. It contains no compilation of methods used in the past in the treatment of glomerular nephritis, nor any detailed criticism of these methods beyond the implicit criticism that runs through the whole argument. We address ourselves to those who feel that in this matter we have not reached the textbook stage and that more investigation is what is needed now. The work done by our out-patient group is necessarily quite inadequate and calls for critical revaluation, both clinical and experimental. It is because it is so provisional and incomplete that we have had to present it in detail. Only thus could we hope that it might be extended and corrected.

We have asked to be heard because we have been subjected to conditions that are like those existing for the practicing physician. It may not seem quite reasonable if we make the same request again on the ground that some of us have spent more time in experimental work on rats than in clinical work with patients. It is true that we were obliged to go far back into general biology and that the relation between our experimental and clinical endeavor was not always obvious. Nevertheless, it was invariably the patients who raised the questions we tried to answer, and it was through combining clinical observations with experimental results that our opinions have been formed, and that the method of treatment we describe gradually attained some clarity of definition.

We include many experiments that have not been published. Ordinarily these would have been described in a series of papers and would have been sent to the technical journals with the names of those who executed the work, but all of us felt that there was some advantage in

having them appear in what we think is their proper clinical contex
They were carried out by Mrs. Evalyn Barrett, Mr. D. D. Lee, Mr. W. Lew, Mr. L. J Poo, Mr. W. D Yuen, and the member of the group whose name appears on the title page of this book because he is responsible for the more speculative clinical sections, and because he has been able to remain a member of the group from its beginning, when it did not have its present composition, and when it was engaged in work that provided an indispensable foundation for this extension into the field of therapeutics.

We have said that the growth of efficiency in medical service depends on the development of well-co-ordinated teams or groups. The truth of this statement has grown sharper and clearer in the course of writing this book, which itself is nothing else than an account of the work of one such group, and an attempt to derive some immediately useful conclusions from what that group has done during the past twenty-five years. It would be pleasant if all those who, at one time or another, have been members of this group could meet again to consider the meaning of what we have done together. We should certainly not accept this book as it is now written but would fall at once to the task of tearing it into shreds. It would be thus that we should re-establish for ourselves the proper atmosphere of the group, which lives always at war with itself, no claim being ever advanced that does not meet its counterclaim, no thesis presented that does not promptly elicit its antithesis. It will always be so, because the group as a whole is not interested in anything that belongs to the past or the present, except to break it up and build, from any fragments of truth and usefulness that may remain, a new bridge into the future. The group still carries on, forever immune to the attempt of any individual within it to crystallize its meaning or bound its activities within the confines of a dogma. The facts it has brought to light will remain long after this particular formulation of their significance has been superseded and is forgotten.

San Francisco, California

T. Addis.

CONTENTS

CHAPTER I

SPECIAL CLINICAL LABORATORY METHODS FOR THE PHYSICAL EXAMINATION OF PATIENTS WITH RENAL DISEASE

HISTORY OF CLINICAL METHODOLOGY

Whenever we try to say anything about the diagnosis of Bright's disease, it will be found that whatever has a strictly clinical, as opposed to a scientific or historical, interest revolves round the methods that should be used in the physical examination of the patient. This is because we are more or less aware that our present methods are inadequate, and we recognize that we cannot solve more complex problems until we have overcome this primary clinical difficulty. Let us consider what happens in the doctor's office, or the out-patient department, when it is reported that the "routine" examination shows that the urine has a "two plus albumin." In a large proportion of such cases the most searching history and the most exhaustive physical examination fail to reveal any abnormality we can link with the proteinuria. What are we to do, then? Even when we find hypertension, edema, anemia, or arteriosclerosis, the relation between these signs and the renal lesion responsible for the appearance of the protein in the urine remains a matter of speculation. It is a question to be decided on grounds of statistical probability, on what pathologists tell us about the frequency of association of various diseases of the kidney, and these extrarenal symptoms we observe. It is not determined by anything we can see for ourselves and really know about the patient.

There is a way out of this seeming impasse. When we see abnormal amounts of protein in the urine we suppose there is something wrong with the kidney. The next question is, "What is the nature of this renal lesion?" We can reasonably expect to find at least the beginning of an answer in the urine. The kidney consists of many nephrons whose glomeruli are filtering fluid from the blood-plasma. As this fluid flows down the tubule there float in its stream any red cells that may have found their way through damaged glomerular capillaries, and any degenerated cells that may have been desquamated from the wall of the damaged tubule. As the filtrate carries on down the long, winding

tubule, it is being rapidly concentrated by the reabsorption of water, and there comes a time when the dissolved protein in the fluid may clot or clump into casts, or the cells may be embalmed within the transparent gels that suddenly form within the lumen of the lower reaches of the tubule. When the urine finally reaches us, it is full of evidence of the sort of disease that involves still-functioning nephrons. This is our principal source material in the development of a renal lesion's history. When the patient dies the kidneys may go to the pathologist, but while he lives the urine is ours. It can provide us day by day, month by month, and year by year, with a serial story of the major events going on within the kidney. The examination of the urine is the most essential part of the physical examination of any patient with Bright's disease.

Nevertheless, it would seem that we have not made much progress in comprehending the nature of the renal lesion of our patients during their lifetime. It is often said, and with some justification, that we have made no real advance in this field since the time of Richard Bright. This relative stalemate on the clinical front is all the more remarkable in view of the great contributions recently made to our understanding of renal physiology and the sure foundation of structural knowledge given to us by the patient work of anatomists and pathologists. What is responsible? We find what it is if we look at the methods we have used in studying renal disease since Bright's time.

Bright used very simple methods. He boiled the urine in a pewter spoon over a tallow candle and, on adding a drop or two of vinegar, he observed that a coagulum appeared. This was not a new observation, but he made a clinical use of it for he followed these patients having albuminuria to the end, and found at postmortem that they had gross evidence of disease of both kidneys. This was the beginning, and has become in a sense the end, of the clinical study of Bright's disease. We still follow Bright's method. The fact that we use a test-tube instead of a spoon and acetic acid instead of vinegar is immaterial. So it is interesting to note that it was Richard Bright himself who made an end of what should have been only a beginning. He knew that the urine contained the answer to his clinical questions but, influenced perhaps by a feeling that the study of the urine was not proper for a physician, or perhaps by a sense that such a matter lay beyond his training and capacity, he turned over all further investigation of the urine to a chemist, "his learned friend, Dr. Bostock." Dr. Bostock sent him a "learned" report, and there the matter ended, as it always will when clinicians try to get other people to answer questions they ought to answer themselves. Dr. Bostock doubtless had his own questions. He was not interested in those of Dr. Bright.

Today it is still true, as it was then, that any clinician who really wants to find something out about a patient with Bright's disease, must himself look at the urine. If he is content to derive his information from laboratory reports he is in the same position as a specialist on diseases of the chest who hires someone to give him a report on auscultation and percussion, or a cardiologist who asks someone to give him an account of the heart sounds of a patient. What the clinician learns when he himself looks is something other and more than that given to him in the finality of any expert's report. However inadequate and even mistaken his observations may be, they are at least his own. They are the beginning of a continuing attempt to answer questions that will be answered only by clinicians using clinical methods. This is the way out of the clinical impasse. We have to develop our own methods for urine examination and do our own work.

If we grant that the lack of adequate methods may be one of the main reasons for the lag in the growth of clinical comprehension in Bright's disease, it will be worth while to note the nature of the methods that have come into use in other fields where progress has been made. We find a variety of tools, e.g., the ophthalmoscope, the microscope, the cardiograph, the x-ray tube. These were made by scientists for scientific purposes. But they have been taken over by clinicians and converted into clinical tools. For the scientists, they are means of measurement, and the clinical scientist still uses them in this way insofar as he is a scientist, but the clinician, insofar as he is a pure clinician, finds them useful in quite another way. They are for him the means whereby he can see what he could not otherwise see; they are instruments for making visible a part of his patient that would otherwise be invisible. Whenever the doctor can use an instrument that allows him to see or feel or hear better, he has the means for clinical advance. It is this help he needs in Bright's disease. He must find some way to see the kidney and observe what sort of lesion there is and how extensive it is. But even though the urine no doubt contains evidence as to the sort of disease in the kidney, and even though we ourselves look at it, an inspection of the urinary sediment makes no constant picture even in the same patient. The ordinary clinical methods may reveal that something is wrong, but what and how much is left obscure.

Faced with this situation the modern clinician, like Dr. Bright, turns to the chemist for help, and the records of his patients are embellished with the results of determinations of the quantities of various materials in the urine and blood. However, these figures have not become a part of the clinician's armamentarium. They do not give him what he wants. The doctor has no use for anything but a picture. He has a different

purpose than does the scientist. Figures are the material of the scientist because the abstraction of number is in consonance with his purpose to exclude what is individual and variable in order to reach toward what is general and constant. But it is just that which is singular about his patient that the doctor wants to see. He strives always toward what is qualitative and particular. He wants to see the stuff itself, not a figure. You may tell a doctor that his patient has a red cell count of 2,500,000 red cells per cu mm, but you tell him much less than he will get by a glance at a centrifuged specimen of his patient's blood, for then he has a vivid, colored picture in which he sees not only about half the usual volume of red cells, but he observes these cells in relation to the layer of leukocytes and platelets, and he sees the plasma above it and notes its color and transparency. He comprehends all this not in the form of numbers but as a part of the picture he is making in his mind as to the disease and the effect of the disease on this particular patient. The blood then becomes an element in everything else he has heard and seen and felt, and it is while all this takes shape and falls together in his mind as a unique, self-consistent composition that the diagnosis is reached and the treatment determined. He recognizes disease just as he recognizes an old friend. He is hard put to it when you ask him how he knows his friend. He may give you reasons, but he cannot give you in words a convincing account of all of his real reason, which is nothing else than that a glance at this man reproduces for him in the flesh the picture of his friend that lay implicit in his mind.

Now the doctor has to be completely absorbed in this endeavor to recognize in his patient some face that he has seen before.[1] He cannot leave the patient in order to undertake the completely diverse discipline of complicated chemical and physical procedures. The doctor is a "seer"; that is, he looks and sees and knows, and all his diagnostic methods should cost him no more effort than a glance. But how shall that be done? How can the multiple component parts of the urine and blood be separated and made visible in their proper relations to one another and to the patient, so that the doctor can look and see and know?

It is because it is hard to do all this that we are left in the dark and are

[1] One is driven to the use of metaphor when trying to describe anything as complicated as diagnosis. Yet, whenever we have selected one parable to illustrate some special aspect of the whole, it becomes at once apparent that it succeeds only by virtue of an unwarranted neglect of other elements in the complex. Thus, we are accustomed to speak of "disease entities" as though they had an independent, individual existence and could be recognized as friends—or better, perhaps, as enemies. This is obviously one of those abstractions that *do violence to the reality of the concrete* situation, for there is no disease apart from the patient. The disease is the change produced in the patient by a pathological process. Diagnosis involves the observation of the patient as he is, and also a reconstruction in imagination of the patient as he was, before he was afflicted. The disease is the difference between these two pictures. But this, also, is an abstraction.

able to do so little for our patients. We have waited long enough in the hope that chemists will do the work for us. They never will, for to do so would be a prostitution of all they are. This is something we have to do for ourselves, and there is no need to be discouraged if first attempts are crude and faulty.

Distinction Between Concentrations and Rates of Excretion of Urinary Constituents

We have all been baffled and left uncertain when we have examined the urine of patients with proteinuria. The trouble is that what we see is always changing, even in the same patient. We should like to infer from the amount of protein and the casts and cells we observe what sort of disease exists in the kidney, but if we begin to do that our very first inference would have to be that the intensity of the disease is undergoing extreme fluctuations from day to day, almost from hour to hour. Since that contradicts all the pathologists tell us about renal disease, we stop then and there, admit our too-simple-minded hope is frustrated, and turn our attention to less direct methods of finding out what is wrong with the kidney.

As an everyday illustration, consider the case of a middle-aged man who comes into the office complaining of morning headaches that wear off during the day. In the course of the examination it is found that his blood pressure is high He is asked to give us a freshly voided specimen of urine. When this urine is boiled and a drop or two of acetic acid is added, a scarcely perceptible haze of coagulated protein is seen. When 15 cc of this urine are centrifuged and the sediment is examined, there is nothing to see but a few epithelial cells. It seems reasonable to suppose that in this patient the headaches may be part of what we call "essential hypertension" and that he does not have glomerular nephritis. But to make sure, he is asked to return the following day and bring the urine he voids when he gets up in the morning Again the urine is boiled and acetic acid is added. This time there is a heavy cloud of precipitated protein, and when the urine is centrifuged the sediment is seen to be rich in casts and cells. We know very well that in such an instance the intensity of the renal lesion has not changed overnight to the degree indicated by what we see in the urine. If we want to find the reason for the discrepancy between our afternoon and morning observations, it would be proper to inquire whether there was any difference in the conditions to which the patient was subjected at these times. If we ask him he will tell us that on the occasion of his first visit he had voided urine just before a 1-P.M. lunch at which he had had a bottle of beer. He came to the office at 3 P.M. just as he was at the height of a diuresis. The 400 cc

of dilute urine he passed in the office was a 2-hr urine representing a rate of excretion of 200 cc per hour. Thereafter, he took nothing more to drink, and the 200 cc of concentrated urine he brought next morning was formed between 10 P.M. when he went to bed and 8 A.M. when he got up. It was a 10-hr. urine representing a rate of excretion of 20 cc per hour. Can the contradiction between the two urinary pictures presented to us have arisen because the afternoon urine was dilute and the morning urine was concentrated?

Such a hypothesis can be tested All we have to do is to take 20 cc of the morning urine, which is a 1-hr urine, and run water into it until it has the 200-cc volume that a 1-hr part of the afternoon urine had. Both urines, secreted during equal periods of time, will thus be diluted to equal volumes, and the only difference will be that in one case the water was run in from the gastrointestinal tract and in the other from the tap. When we test the now diluted morning urine we will find the heavy cloud of protein is transformed into a faint haze. If we look at the centrifuged sediment quickly, we may see the red cells swelling and disappearing and may watch the hyaline casts dissolve until we have again only the epithelial cells we saw yesterday afternoon. When the times and volumes are equalized, we find that the proteinuria and the sediment are the same.

This sort of observation, which can be made almost any day in any doctor's office, is enough to show that there is something wrong with the methods that we and the clinical laboratories use. We are acting as though we could employ for the urine the same technique that we find useful in dealing with blood. With blood, the measurement of concentrations suffices because the total blood volume remains about the same from day to day. But when we look at the concentrations of the materials dissolved or suspended in urine we get only confusing and apparently contradictory results because the urine volume is not constant but extremely variable. It is always changing in order that the blood volume may remain constant. The first step toward a reasonable method of urine examination requires the recognition of this obvious physiological fact. The concentration of any substance we separate from the urine, *i.e*, the quantity per cubic centimeter, per 100 cc, or per 1,000 cc will change with every variation in urine volume. But its rate of excretion, i e., the quantity found per minute, per hour, or per 24 hr will remain relatively constant. Thus, we find that we can get a fiftyfold change in the concentration of protein by getting patients to reduce their urine volume by abstaining from fluids, or to increase it by water drinking, and yet through all these changes, the rate of protein excretion remains substantially the same.

How Patients Can Give Us Timed Collections of Urine

If we are to measure rates of excretion instead of concentrations, we shall have to ask our patients to give us the total urine formed over a known period of time. To many it will seem that we are asking too much. Especially will this seem a Utopian idea to those who know how *hard it is to get exactly timed urine collections from patients in a hospital* ward, even with the help of many willing nurses. However, the difficulty in that situation arises because our nurses are "trained." They have been taught to chart the temperatures and pulse-rates of twenty to thirty patients as having been taken at exactly 8 o'clock, whereas, in fact, they were measured any time between 7:30 and 8 30. It is only natural that any conscience they may originally have had with respect to timing should have been drilled out of them.

Our patients, however, have not been trained. Furthermore, they have a personal interest in making sure that no mistake is made. In their case there is no educational difficulty. All we have to do is to provide them with the material means required for carrying the urine, and we will get precisely timed urine collections. The means consists of a cheap, glass, quart bottle. It has a wide neck and it is securely stoppered by a No. 9 rubber stopper, if it can be obtained. If not, a screw-topped bottle will suffice. The bottle has been thoroughly rinsed with distilled water in order to remove the fauna and flora of the city tap water. It is placed upside down on a wire rack, and after all the water has drained out, a few drops of 40% formaldehyde—just enough to wet the inside of the bottle—are added to prevent the growth of organisms that may be present in the urine. After the rubber stopper has been jammed in and the bottle wrapped in paper, it can be put aside for an indefinite time until the patient needs it.

When we centrifuge out hyaline casts and red blood-cells from a concentrated urine, remove the supernatant urine, add water, and centrifuge again, we find that the hyaline casts have disappeared and that only a few faint shadows of lysed red cells remain. When we ask a patient, in whose urine we have just found hyaline casts and red blood-cells, to drink a lot of water, we find that the dilute urine he presently gives us no longer contains hyaline casts and has only a few faded red cells left. Hyaline casts, with the inclusions they trap as they form in the lumen of the tubules, and the red cells that come all the way from the glomeruli, are useful to us in our attempt to construct from the urinary sediment a picture of the renal lesion. But we cannot always get from all our patients a urine so concentrated that hyaline casts and red cells will remain undissolved. By the time advancing disease has destroyed half of

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HOW PATIENTS CAN GIVE US TIMED COLLECTIONS OF URINE

If we are to measure rates of excretion instead of concentrations, we shall have to ask our patients to give us the total urine formed over a known period of time. To many it will seem that we are asking too much. Especially will this seem a Utopian idea to those who know how hard it is to get exactly timed urine collections from patients in a hospital ward, even with the help of many willing nurses. However, the difficulty in that situation arises because our nurses are "trained." They have been taught to chart the temperatures and pulse-rates of twenty to thirty patients as having been taken at exactly 8 o'clock, whereas, in fact, they were measured any time between 7.30 and 8:30. It is only natural that any conscience they may originally have had with respect to timing should have been drilled out of them.

Our patients, however, have not been trained. Furthermore, they have a personal interest in making sure that no mistake is made. In their case there is no educational difficulty. All we have to do is to provide them with the material means required for carrying the urine, and we will get precisely timed urine collections. The means consists of a cheap, glass, quart bottle. It has a wide neck and it is securely stoppered by a No. 9 rubber stopper, if it can be obtained If not, a screw-topped bottle will suffice. The bottle has been thoroughly rinsed with distilled water in order to remove the fauna and flora of the city tap water. It is placed upside down on a wire rack, and after all the water has drained out, a few drops of 40% formaldehyde—just enough to wet the inside of the bottle—are added to prevent the growth of organisms that may be present in the urine. After the rubber stopper has been jammed in and the bottle wrapped in paper, it can be put aside for an indefinite time until the patient needs it.

When we centrifuge out hyaline casts and red blood-cells from a concentrated urine, remove the supernatant urine, add water, and centrifuge again, we find that the hyaline casts have disappeared and that only a few faint shadows of lysed red cells remain. When we ask a patient, in whose urine we have just found hyaline casts and red blood-cells, to drink a lot of water, we find that the dilute urine he presently gives us no longer contains hyaline casts and has only a few faded red cells left. Hyaline casts, with the inclusions they trap as they form in the lumen of the tubules, and the red cells that come all the way from the glomeruli, are useful to us in our attempt to construct from the urinary sediment a picture of the renal lesion But we cannot always get from all our patients a urine so concentrated that hyaline casts and red cells will remain undissolved. By the time advancing disease has destroyed half of

the total number of nephrons, there begins an unmistakable drift toward a dilute urine, even when no fluids have been taken for some time. When *two-thirds or more of the nephrons are gone, the urine is dilute even when the patient begins to be dehydrated. In such patients it is not only useless but positively detrimental to their welfare to ask them to try to get a concentrated urine by abstaining from fluids. They all have blood urea and creatinine concentrations well above the normal levels; this condition and their dilute urine may be the only indications of the extent of their renal lesion. So, when a new patient comes, we determine his serum creatinine concentration before we ask him to concentrate.*

It saves time to give the patient a mimeographed copy of the instructions below for the collection of a concentrated urine. The blank spaces are left for insertion of the day on which we want the patient to do without fluids and for the time that may be convenient for him.

DIRECTIONS

1. *After breakfast on* ——— *take no fluids* of any sort *until* next morning. This means no coffee, tea, soup, milk, etc., as well as no water. In all other respects follow your usual habits as regards food.
2. That evening, before going to bed, void urine and throw it away. Do not pass any urine for some hours before going to bed so that you may have no difficulty in emptying the bladder completely. Write the time of voiding on the label on the bottle.
3. Next morning, *when you get up, collect all the urine directly in the bottle.* Write the time on the label.

This degree of abstention from fluids does not lead to any discomfort if the patient is warned not to take much salt on that day. It should be remembered, however, that this plan is designed for the cool weather of San Francisco, and that in places where it gets hot it would be too severe a restriction. In that case we ask the patient to take no more fluid than is required to prevent great thirst.

There are two ways of examining a urinary sediment. There is the traditional way, which we may call *qualitative. And there is the way by which we can make all urinary sediment pictures directly comparable with one another, which may be called quantitative because we can derive from it the rates of excretion of the formed elements. These methods supplement one another and should be used together.*

Qualitative Examination of Urinary Sediment

When urine stands in a bottle, the casts and cells at once begin to fall to the bottom; therefore, just before taking a sample for examination, the urine should be mixed by inverting the bottle *after ramming in the*

rubber stopper. A centrifuge tube is filled to the 15-cc mark with mixed urine. This is centrifuged until all the formed elements are packed at the tip. The major portion of the supernatant urine is removed with a 15-cc pipette provided with a rubber suction bulb, and the last cubic centimeter or so is taken off with a capillary pipette. The sediment thus concentrated in a drop at the extreme tip of the tube is then taken up in the pipette and transferred to one side of a blood counting chamber. If, after centrifuging, it is seen that the sediment is contained in a compact mass of mucus, the supernatant urine can be decanted. In that case the tube must be maintained in the inverted position and the sediment at the tip removed by a capillary pipette introduced from below, for if the tube is brought back to the perpendicular position the urine on the sides of the tube will run down and dilute the sediment.

It is obvious, however, that judgment is required in preparing the qualitative sediment. There are alkaline urines with amorphous phosphate deposits. The urine must then be acidified before it is centrifuged. There are acid urines in which urates have separated. The urates must be dissolved by heating the tube in hot water before the urine is centrifuged. There are urines with so much pus and blood that no detail can be distinguished under the microscope until the sediment has been diluted with salt solution. On the other hand, there are instances in which there is so little sediment that essential qualitative facts will be missed unless steps are taken to attain a still greater concentration than the above method provides. This is particularly true in patients with latent glomerular nephritis, in whom no certainty as to diagnosis can be obtained unless the very few blood-casts they form are found, or in patients in whom the time of complete healing of a glomerular nephritis requires the demonstration that their urine contains no red blood-cells. In such cases the total urine collection is allowed to stand for 1 hr or more until the formed elements have fallen to the bottom of the bottle. A 15-cc pipette is then introduced and moved over the bottom of the bottle to remove the lowest part of the urine. Four such samples are centrifuged and examined either in the blood counting chamber or on ordinary slides, depending on the physical characters of the sediment thus obtained. In this manner it is possible to be sure that nearly all the formed elements in any given collection of urine have been seen. There are also cases in which the best method is to examine a freshly voided urine because, if it is centrifuged while it is still warm and before any mucus has separated out, the formed elements pack at the extreme tip of the tube and can thus be obtained in the most concentrated form.

It will be obvious, also, that an adequate qualitative examination of the urine sediment may require the intelligent co-operation of the

patient. There are instances of pyuria in which some indication of the site of origin of the pus cells is obtained by getting the patient to empty his bladder into two bottles; there are cases of bacteriuria in which the collection of short-time specimens under induced diuresis may give information; there are circumstances under which it is essential to obtain a catheterized specimen of urine; and there are many conditions that require from the patient the collection of precisely timed collections of urine under known conditions of fluid consumption, of changing position of the body, and of alternations of rest and activity.

Quantitative Examination of Urinary Sediment

The time over which the urine is formed is taken as the basis of comparison, and it is convenient to take ⅕ of 1 hr urine. The patient has noted on the bottle label the time at which the collection was started and the time at which it was completed. The difference between these times is the time over which the urine was secreted. This, and the volume of urine, are the only requirements for the derivation of ⅕ of 1 hr urine. The volume is measured so as to avoid foaming, but if foam prevents a precise reading, a drop of caprylic acid may be added. A strip of celluloid is placed on the abscissa of the appended chart, so that the celluloid is vertical to the line indicating the time during which the urine was collected.

Another strip of celluloid is then placed at the point indicating the volume, which has just been read. The diagonal line that runs through the point of interception of the vertical and horizontal lines is followed out to the right-hand margin of the chart. There will be found the volume of urine that represents ⅕ of 1 hr urine in cubic centimeters. This number ascertained, the urine is returned to the bottle, the stopper reinserted, and the urine is mixed by inversion just before the required amount is transferred to a 15-cc graduated centrifuge tube. A slide rule is a little more precise and just as quick for those who are accustomed to its use, but in any event the important point is to avoid arithmetical work that takes time and is so often fraught with error. When the urine volume is large, ⅕ of 1 hr urine may be more than 15 cc. In that case both the time and the volume are reduced to one-half, but the same picture is obtained by reducing the volume in which the sediment is mixed to 0.25 cc instead of 0 5 cc.

Centrifuging for 5 min at 1,750 rpm or for 3 min at 3,500 rpm is sufficient to bring all the formed elements into the tip of the tube. Half of the supernatant fluid (⅒ of 1 hr of urine) is then transferred by a capillary pipette to another graduated tube and put aside for the protein determination. The remaining urine above the sediment is taken off with

a capillary pipette until the volume is reduced to 0.5 cc. The sediment at the tip of the tube is then thoroughly mixed in this ½ cc by repeatedly drawing it into the pipette and expelling it into the tube, and, without giving any of the formed elements time to settle out, a drop is transferred to the other side of the blood counting chamber from that in which the qualitative sediment has been placed. The blood counter is put on the

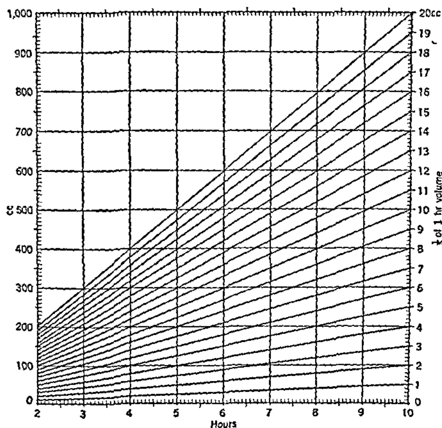


Fig. 1

movable stage of the microscope, and after the ruled area has been focused under the low power the sediment is ready for inspection by the doctor.

What is seen under the microscope on the quantitative side is the rate of excretion of the formed elements in the urine. This rate is not influenced by the volume of the urine; that variable was removed at the beginning because we took a proportionally larger volume from a dilute than from a concentrated urine. Furthermore, what is seen in the sedi-

ment of one patient is directly comparable with what is seen in the urine from any other patient. It is because the method enables us to make direct comparisons between one patient and another that we can call it a clinical method.[2] In this respect it is on a level with our other methods, with x-ray pictures, electrocardiograms, or what we see when we use an ophthalmoscope. It is like them, too, in that the most essential information can be obtained at a glance. It is not necessary for the doctor to take the time to determine the precise number of casts and cells, but he must look at the sediment and form his own ideas as to the nature and intensity of the renal lesion. If he begins to depend solely on the figures given to him by the laboratory worker the unity of the group will be lost, and that corroding disease of modern medicine, the separation between the doctor and the laboratory worker, will at once begin to diminish the therapeutic efficiency of the group.

It is not that the enumeration of the number of formed elements is unimportant. But, in general, quality belongs to the doctor, quantity to the laboratory worker. So it will often happen that the doctor will spend more time looking at the qualitative than at the quantitative sediment. Indications as to the nature of the disease are sometimes found there that do not appear at all on the quantitative side. This is because the dilution is so great that elements present in relatively small numbers will probably not be represented at all in the quantitative picture. It is this fact that makes it unnecessary to have any standard for normal rates of excretion of casts and cells. It is true that people with no renal lesion excrete, on the average, 2,000 hyaline casts, 130,000 red blood-cells, 650,000 epithelial and white blood-cells, and 10 mgm of protein every 24 hr. These figures have a theoretical significance as showing that the signs we are accustomed to take as evidence of disease are present in some degree in "healthy" individuals and that there is thus no absolute separation between health and disease, but they have no practical meaning since, under the conditions we have chosen, the "normal" approaches zero. We shall see nothing or next to nothing in the volume inspected on the quantitative side unless renal disease, and disease of a certain intensity, is present. Now and then it might happen that we come across a red cell, or even, conceivably, a hyaline cast in a normal urine, but that accident would only make it necessary that we go further and look at several unit volumes. If we want to use it in that way, the method is capable of giving us any degree of precision that our special purpose requires or that our patience will tolerate.

[2] The principle of presenting the urinary sediment of the patient as a picture directly comparable with that of any other patient was first put into practice in 1934 by Henry Gibbons III. (I) although the application was in another form than the one we here describe.

In every case, whether there is much or little or nothing to be seen in the quantitative sediment, we must look at the qualitative side to be sure we are not missing anything. Even a short inspection as the field is changed by the movable stage is sometimes rewarded by the appearance of some element that has a more or less pathognomonic significance—a renal failure cast, an "oval fat body," or a blood-cast; and when casts are not numerous on the quantitative side, it is in the qualitative sediment that a differential count of the various sorts of casts can easily be made.

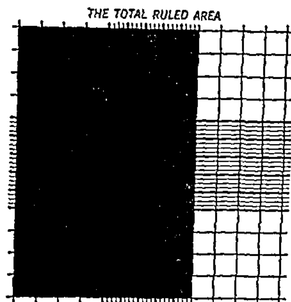
It would be wrong, however, to give the impression that the counting of a urinary sediment is such a complicated and laborious process that the doctor will never have time for it. Actually, a count takes no more than a minute. The accompanying diagram reproduces the rulings on a blood counting chamber, and the two shaded areas are the unit areas for counting—the larger one for casts counted under the low power, and the smaller for cells counted under the high dry power. No calculation is necessary, because the casts seen in the volume over 1 unit area, multiplied by 100,000, comprise the number of casts excreted in 24 hr, and the red cells or epithelial cells that might be tubule cells seen over the smaller unit area, multiplied by 1,000,000, give their 24-hr rates of excretion.

This gives the impression that the method is one of extreme simplicity and ease of operation. This is true, after certain small technical difficulties have been overcome. Hyaline casts are transparent, and their refractive index is so close to that of glass that they are invisible unless the light is dim, therefore the Abbe condenser must be racked down to the lowest point possible and the iris nearly closed. Once the proper lighting has been obtained, an approximate cast count can be made in a few seconds.

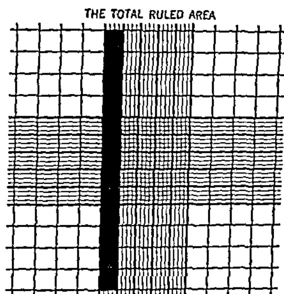
When the casts have been counted the high dry lens is turned on. The field will then be quite dark. The Abbe condenser must be raised and the iris opened a little, but the light should still be subdued or we shall look through the red cell shadows and be unable to see the details of the structures embedded within the casts.

Color now becomes important. If artificial light is used, it should pass through a thick, daylight filter because the usual electric lamps give a light that is too yellow. The blood counting chamber must be made of ordinary glass, not of the amber-colored glass that makes it hard to see hemoglobin in cells and casts.

In *counting the epithelial cells, it goes without saying that* we pay no attention to the large, squamous cells from the surface of the urinary tract or any other cell that could not possibly be a renal cell; but we are obliged to enumerate pus cells and doubtless also some cells from the



The Six Large Squares That Are Shaded Constitute the Unit Area For Casts.
Over It Lie 0 0006 cc Of Urine



The Shaded Area Is the Unit Area For Cells.
Over It Lie 0 00006 cc Of Urine

Fig. 2

deeper layers of the mucous membrane of the tract because, for all we can tell, they might have come from the kidneys. It is true, of course, that pus cells are, in general, smaller than tubule cells, but the range of size of tubule cells is considerable. Sometimes they are as small as pus cells, but when they are swollen with fat they may have a diameter many times greater than a pus cell, so we are obliged to include all the cells that range from, say, 8 to 30 microns in diameter. It is dangerous to be specific, for a cell that in one sediment should certainly be excluded because it is too large will properly be included in the count made on another.

When the doctor looks at the quantitative sediment, he has to see it always under the precise conditions we have described because, if any other dilution is used, the picture will be distorted. There is no such limitation imposed on the laboratory worker. It is quite important that he should freely adapt the method to his quantitative purposes Take, for instance, the case of a patient with glomerular nephritis At the very beginning, if the directions given are followed, the sediment will appear as an almost solid mass of red cells, tubule cells, and casts. This is in itself instructive, but no count can be made until the 0.5-cc volume is diluted with normal salt solution to 5, 10 or 15 cc. Furthermore, the degree of dilution required for the casts will be less than that needed for the cells, and the laboratory worker will have to pick the one he finds most convenient. A year later, in the same patient, there may be a question as to whether the lesion has wholly healed When the doctor looks at the sediment from ⅕ of 1 hr urine diluted in 0 5 cc, he will see no cells or casts in the few fields at which he looks. This tells him that any lesion that is left is, at most, minimal, but he will not conclude that complete healing has occurred He will wait to hear from the laboratory worker. The method will then be modified again. Another ⅕ of 1 hr sample will be centrifuged, but this time the volume in which it is mixed will be 0.1 cc instead of 0.5 cc and the number of unit areas that are counted will be multiplied until the laboratory worker is satisfied.

When people begin to look at urinary sediments, they naturally want first of all to make sure they will recognize a cast or a red cell or a possible tubule cell when they come across one. They will point to some particular structure and ask, for instance, whether that is a red cell. They are apt to be surprised, and perhaps become discouraged or skeptical if the answer given by those who have experience is, "It may be a red cell, but one can't be sure" Yet that is the only possible answer that can be given from the most careful study of that isolated cell. The answer lies not there but elsewhere—beyond that cell, in the rest of the

sediment. If, on moving the counter, we see other cells that are like it but are more clearly red cells, the question mark attached to that particular structure begins to fade. If, next, a blood-cast comes into view, the question will for practical purposes disappear. We will then call it a red cell, not on account of anything we find in the cell itself, but because it is seen in the "right company."

To the logical positivist, and to all who can be satisfied only with yes or no answers, this general attitude will appear shockingly casual—perhaps scarcely honest. But the doctor is not a positivist and he cares nothing for red cells or for the whole urine as such. They are only means to his end, which is action, not knowledge. He expects no absolute assurance at any one point. He accepts uncertainties and is content if possibilities begin to support one another and grow into probabilities. It is true that, for certain purposes that are on the border line between medicine and science, he counts casts and red cells and epithelial cells separately, as though they were distinct entities. In the sediment, however, they are together, and together they form for him a picture whose significance depends on their interrelationship. The considerable assurance he may in the end acquire about the nature of the renal lesion does not derive from certainties about any detail; it rests on his recognition that all these fragmentary observations are falling together into a pattern he recognizes—one that fits into a still larger composition that includes all he has heard and seen and felt about his patient.

Determination of Rate of Protein Excretion in Urine

The first step is to find whether there is any measurable amount of protein in the urine, and, if there is, to get a rough idea as to its concentration. There are pitfalls in every qualitative test, but perhaps the most reliable is also the simplest. Add about 3 drops of 20% sulphosalicylic acid to every cubic centimeter of urine used. If possible the sample used should be clear. It is convenient to use the supernatant urine over the qualitative sediment because anything that can be centrifuged has been spun out. If it is cloudy with bacteria, a control tube to which water instead of sulphosalicylic acid has been added should be prepared for comparison. When the protein precipitate is heavy, we can be sure that there is enough to allow us to use a 15-cc graduated centrifuge tube in determining the rate, and when there is only a slight turbidity we know that we shall have to use special, finely graduated tubes to get a measurable reading. No more precise judgment is possible without taking the volume of urine into account.

Here we shall consider only the method in which we start with the $\frac{1}{10}$ of 1 hr urine that has already been transferred from the supernatant

urine over the quantitative urinary sediment. This volume is diluted to the 7-cc mark with water and Tsuchiya's solution (phosphotungstic acid in acid alcohol) is run in to the 14-cc mark. The tube, stoppered with the thumb, is then inverted three times, each time allowing all the fluid to run out of the tip of the tube, so that before centrifuging there shall be complete mixing The tube, balanced with another containing water, is placed in the holder of a Fisher "Safety" centrifuge. After the clock in the circuit has been set at 5 min, the run is started. The motor of this centrifuge operates only at 1,750 rpm, and this gives the constant speed that, with constant time, is required if the volume of precipitated protein is to be translated into terms of grams of protein excreted per 24 hr. Temperature also must be a constant, for protein precipitates expand on cooling and contract on warming, but this requirement is met in the appended conversion tables which provide a temperature correction derived from a reading of the room temperature at the end of the run. Since the centrifuge is angled, the surface of the precipitate is also angled, and for ease of reading the tube should be placed in the holder so that the mid-point of the slope bisects the line of graduation marks.

The tube, with its compactly precipitated protein, is then shown to the doctor. All he has to do is to glance at it. He is looking always at the protein from $1/10$ of 1 hr urine If he imagines this volume multiplied 240 times, he can visualize the volume of protein lost by the patient in 24 hr. He does not need to read the graduation and translate it into grams of protein per 24 hr. He sees about how much there is and, for the moment, that is enough. The measurement can be left to the laboratory worker. If it is any considerable amount, the doctor will hear the exact quantity when the group gets together with the patient to discuss how much food protein he should take.

When the urinary sediment and the rate of protein excretion have been both seen and measured, the essential minimum in the examination of the urine is done More can be done, and much more can be learned, but that can safely be left to the initiative of the laboratory worker and to the specific problems that will come up in the course of the examination of different patients. There is one other point that should be emphasized. This is a co-operative enterprise and is the work not of an individual but of a group. There cannot be any physical separation between the members of the group without a loss in unity of action. The place in which the patient is examined has to be both a doctor's office and a laboratory. This does not mean, of course, that it is necessary that everyone in the group should hear all of the history or be conversant with every detail of the physical examination. There may be

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blood to fill another Wintrobe tube if we want to measure the sedimentation rate. The rest of the blood in the syringe is transferred to a 15-cc centrifuge tube and placed at once in a water bath kept at 37° C. The *coagulation time and the clot reaction can, if they are wanted*, be measured, but the principal reason for keeping the blood at body temperature is to induce the maximum rate of coagulation so that, without delay, we can separate the clot from the glass, spin the blood for a few minutes, and thus obtain the serum we need for the clinical creatinine determination and the measurement of the total serum protein concentration.

The relation between the volume of red cells after centrifuging for 5 min at 1,750 rpm and the volume of red cells at "complete packing" obtained by centrifuging for 30 min at 3,000 rpm (Wintrobe method) is given in Figure 3.

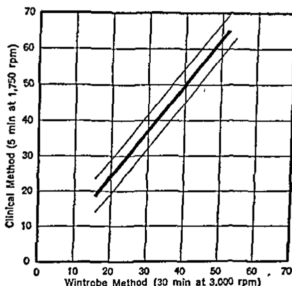


Fig. 3

This relation was established by noting the volumes obtained with this 5-min clinical method on 492 of our patients with varying degrees of anemia, and then centrifuging the same Wintrobe tubes for 30 min at 3,000 rpm and noting the volume at complete packing. The clinical 5-min red cell volume is equal to 1.3 times the Wintrobe red cell volume less 1.35 units of the Wintrobe scale. The correlation ratio is 0.97. The lines drawn parallel to the line of relation are two standard errors

centrifuge into which a 5-min. clock will be built. The error of the determinations would be lessened if the speed could be increased Such a centrifuge would have a wide field of clinical usefulness in providing a visual quantitative presentation of many other substances than those for which we have used the principle of constant speed and constant time.

TABLE 2

THE 5-MIN HEMATOCRIT

CONVERSION OF RED CELL VOLUMES TO PERCENTAGES OF NORMAL VOLUMES*

male: red cell reading	male: % of normal	female: red cell reading	female: % of normal
1.6	33	1.6	37
1.7	34	1.7	39
1.8	36	1.8	40
1.9	37	1.9	41
2.0	39	2.0	43
2.1	40	2.1	45
2.2	42	2.2	47
2.3	44	2.3	49
2.4	45	2.4	50
2.5	47	2.5	52
2.6	48	2.6	54
2.7	50	2.7	56
2.8	51	2.8	51
2.9	53	2.9	60
3.0	54	3.0	61
3.1	56	3.1	63
3.2	58	3.2	65
3.3	59	3.3	66
3.4	61	3.4	68
3.5	62	3.5	70
3.6	64	3.6	72
3.7	65	3.7	73
3.8	67	3.8	75
3.9	69	3.9	77
4.0	71	4.0	79
4.1	72	4.1	80
4.2	73	4.2	82
4.3	75	4.3	84
4.4	77	4.4	86
4.5	78	4.5	88
4.6	80	4.6	90
4.7	82	4.7	91
4.8	83	4.8	93
4.9	84	4.9	95
5.0	86	5.0	97
5.1	88	5.1	99
5.2	89	5.2	100
5.3	91	5.3	102
5.4	92	5.4	104
5.5	94	5.5	106
5.6	96	5.6	107
5.7	98	5.7	109
5.8	100	5.8	111
5.9	101	5.9	113
6.0	102	6.0	115
6.1	103	6.1	117
6.2	105	6.2	118
6.3	107	6.3	120
6.4	108	6.4	122
6.5	110	6.5	124
6.6	112	6.6	125
6.7	114	6.7	127
6.8	115	6.8	128
6.9	117		
7.0	119		
7.1	120		
7.2	121		
7.3	123		
7.4	125		

* Red cell volume, expressed as % of normal average.

fuge tube, taking care to avoid parallax errors. A diluted alkaline picrate is then prepared in a graduated centrifuge tube by adding 1 cc of 10% NaOH to 5 cc of a solution of purified picric acid, which contains 1.75 gm of picric acid per 100 cc, and adding water to the 12-cc mark. After mixing, this picrate solution is added with a capillary pipette to the serum until the 1.5-cc mark is reached. The mixture is then poured into a small test-tube [5] and an interval timer is set to ring 6 min later. In a few minutes the matching of the color against potassium dichromate solutions can be begun, but the color is constantly deepening and the

TABLE 4

POTASSIUM DICHROMATE CONCENTRATIONS (MGS POTASSIUM DICHROMATE DISSOLVED IN WATER AND BROUGHT TO 100 CC VOLUME). THESE CONCENTRATIONS HAVE COLORS THAT ARE EQUIVALENT TO THE COLORS OBTAINED BY THE DIRECT AND FILTRATE CLINICAL METHODS *FROM SERA CONTAINING THE GIVEN CONCENTRATIONS OF CREATININE* (MGS CREATININE PER 100 CC OF SERUM).

DIRECT METHOD				FILTRATE METHOD			
potassium dichromate mgs per 100 cc	serum creatinine mgs per 100 cc	potassium dichromate mgs per 100 cc	serum creatinine mgs per 100 cc	potassium dichromate mgs per 100 cc	serum creatinine mgs per 100 cc	potassium dichromate mgs per 100 cc	serum creatinine mgs per 100 cc
200	0.47	2000	5.24	50	0.27	950	4.35
225	0.54	2250	5.77	75	0.48	975	4.41
250	0.64	2500	6.24	100	0.57	1000	4.50
275	0.73	2750	6.68	125	0.72	1250	5.43
300	0.80	3000	7.10	150	0.84	1500	6.21
325	0.89	3250	7.50	175	0.99	1750	6.96
350	0.98	3500	7.90	200	1.14	2000	7.62
375	1.06	3750	8.28	225	1.29	2250	8.28
400	1.15	4000	8.62	250	1.41	2500	8.91
425	1.24	4250	8.96	275	1.56	2750	9.48
450	1.31	4500	9.28	300	1.65	3000	10.05
475	1.41	4750	9.59	325	1.74	3250	10.68
500	1.48	5000	9.88	350	1.89	3500	11.22
525	1.57	5250	10.18	375	2.01	3750	11.82
550	1.64	5500	10.43	400	2.10	4000	12.39
575	1.73	5750	10.71	425	2.19	4250	12.99
600	1.80	6000	10.97	450	2.31	4500	13.44
625	1.87			475	2.43	4750	14.10
650	1.95			500	2.49	5000	14.64
675	2.03			525	2.61	5250	15.18
700	2.10			550	2.73	5500	15.69
725	2.18			575	2.88	5750	16.23
750	2.44			600	2.94	6000	16.71
775	2.33			625	3.03	6250	17.22
800	2.40			650	3.15	6500	17.73
825	2.47			675	3.24	6750	18.15
850	2.53			700	3.36	7000	18.60
875	2.61			725	3.45	7250	19.08
900	2.69			750	3.54	7500	19.56
925	2.76			775	3.69	7750	20.01
950	2.82			800	3.81	8000	20.46
975	2.89			825	3.84	8250	20.88
1000	2.96			850	3.99	8500	21.36
1250	3.59			875	4.08	8750	21.72
1500	4.15			900	4.17	9000	22.17
1750	4.71			925	4.29	9250	22.59

[5] It is necessary to pick tubes 4 in. by ½ in. that are made of the same glass and that have the same diameter.

final judgment has to be made when the bell rings. The creatinine concentrations, in mgm per 100 cc of serum, that correspond with the potassium dichromate standards are given in Table 4.

When the serum is lipemic or is colored with hemoglobin or bilirubin we have to get a water-clear filtrate after heat precipitation of the serum proteins. Transfer serum to the 1.5-cc mark of a 15-cc graduated centrifuge tube with a capillary pipette. Add an 0.5 molar sodium acetate-acetic acid solution with a *p*H of 5 to the 4.5-cc mark on the tube. Invert to mix. Stopper with a vaccine stopper through which a hypodermic needle is inserted. Leave in boiling water for at least 3 min. Filter through as small a filter as possible into another 15-cc tube. When a little more than 1 cc of filtrate has run through, remove the filter and, with a capillary pipette, reduce the quantity to exactly 1 cc. To thi volume of filtrate add 0.5 cc of a freshly prepared and well-mixed undiluted alkaline picrate solution prepared by adding 1 cc of 10% NaOH to 5 cc of the same picric acid that is used in the direct creatinine method. Set the interval timer to ring at 10 min and make the reading at that time by comparison with another set of dichromate solutions. The translation of the color into creatinine concentrations is given in Table 4.

reliable and precise for safety and yet not so time-consuming and laborious as to make it impractical for patients who, for the most part, feel quite well and are at work.

Before the method is discussed we have to decide what we mean by an adequate but not much more than adequate protein consumption. For adults on diets that contain sufficient calories to cover their energy needs we start by assuming that it is about 0.5 gm of protein per kilogram of body weight per day; that is, 30 gm for a 60-k man, 35 gm for a 70-k man, and 40 gm for an 80-k man. We take this figure from Sherman's compilation of the results of many experiments that were designed to find the least amount of protein on which nitrogen equilibrium could be obtained (5). This rule of 0.5 gm per kilogram of body weight is useful as giving the order of magnitude of what can be considered an adequate but no more than adequate protein consumption, but it would be a mistake to suppose it can give us more than a general orientation. This figure is an average. There were experiments in which nitrogen equilibrium was obtained with as little as 0.4 gm per kilogram, and others in which as much as 0.6 gm per kilogram was needed. Furthermore, it might, with good reason, be objected that it is quite unlikely that the minimum protein requirements vary directly as the body weight varies, and that this mode of expression probably will lead to an overestimate of the needs of big men and an underestimate of those of little men. There is reason also to suppose that this average of 0.5 gm of protein per kilogram of body weight is too high because many of the older experiments were carried out before we knew about vitamins, and the conditions may not have been favorable for the attainment of nitrogen equilibrium.[1] Nevertheless, for adults, this is as good as estimate as we can get at present, and we can use it at least as a point of departure.

Children may have a higher rate of protein metabolism than adults, and some additional protein is needed for the formation of new body protein, though, in theory at least, the quantity needed for growth is very small. Here there is even less precise knowledge than in the case of adults. We have seen growth in children in the second decade on as little as 0.5 gm of protein per kilogram, but we are accustomed to assume that the minimum may be about 0.6 gm and, during the first 2 yr of life, about 0.75 gm of protein per kilogram per day. These are only guesses. In each patient the question as to whether he is getting an adequate amount has to be determined on the basis of clinical observation.

[1] This supposition has just been validated by a group working in the Department of Nutrition of Harvard University. In a careful study on twenty-six normal individuals they find an average protein minimum for maintenance of a little less than 0.4 gm. of protein per kilograms of body weight (6).

VITAMIN SUPPLEMENTS

Our objective is to reduce the protein content to a safe minimum, leaving all the other constituents as much above the minimum requirements as the patient desires. But whenever we interfere with one element the others are liable to be altered too, which is the reason why dietetics is an all-or-nothing affair and why we cannot rest content with changing only the amount of protein in the diet. The B-complex vitamins are found in nature wherever there is life and growth, and life and growth go along with protein. So a diet that contains no more than the minimum amount of protein may be one in which there is an inadequate supply of B complex, even though the diet contains more than an adequate supply of calories. This is probably more true today than in the past because there are now so many highly purified carbohydrates and fats that are widely used as foods. There are probably not many clinical situations in which pure vitamin supplements are necessary, but we think this may be one of them, so we never ask a patient to reduce his protein consumption without adding B complex in some form or other,[2] and, in children, we always add A and moderate doses of D.

MINERAL SUPPLEMENTS

A diet with less than the usual amount of protein is apt to have less than the usual amount of minerals This whole question of mineral requirements is only beginning to open up. It has been shown that there is a grave danger of an inadequate calcium intake and so all children and many adults are asked to take calcium just before they go to bed, that time being the one at which the calcium is least likely to find itself in the presence of phosphate from digested food, which, in the alkaline duodenum, would precipitate it as the insoluble triphosphate. This is to prevent a possible phosphorus deficiency. Sodium, on the other hand, has a positive as well as negative value in the dietetic treatment of renal disease, for sodium consumption determines water consumption. Our purpose is to decrease the osmotic work of the kidney. One of the factors in the work of the kidney is the ratio between the concentrations of urinary constituents in the urine and the plasma (page 225). We shall later give reasons for the belief that urea is the urinary constituent that ordinarily requires most work from the kidney, and, for urea, the greater the volume of urine the less work the kidney has to do in producing the urine. For this as well as other reasons, we think that many of our

[2] Yeast is the cheapest source of B complex, but it contains so much nucleic acid that we are afraid to use it. Wheat germ is better, but it contains 35% of protein and probably some purines. We therefore use one or another of the pharmaceutical preparations.

patients should excrete every 24 hr, more than 3,000 cc of urine. We are not at all sure that it is safe to get this urine volume by "forcing fluids." We prefer to encourage the patient to take plenty of salt, and to leave the water drinking to his natural inclinations, for if he takes 15 gm of salt a day he will ordinarily take enough fluid to provide a 3,000 cc urine volume in 24 hr. When our patients with glomerular nephritis become edematous, and in some patients with hypertension who still have a lot of efficient nephrons, we may, for a time, do just the opposite and reduce sodium consumption to a minimum. In the edematous patient we actually have no choice, for any salt that is given is held in the tissue spaces and its only effect is to make the patient more waterlogged.[3] As soon as his weight becomes stationary we add small amounts of salt, and increase these amounts if the salt is excreted. In these edematous patients we have to remember that there is no reason to restrict minerals other than the salts of sodium. If we do not take pains to add these other minerals there will be a double danger of deficiency: one is a consequence of the low protein intake and the other arises from the fact that a low sodium diet is apt to be low in all minerals.

Later on in the course of glomerular nephritis, and indeed in all patients who become uremic, the mineral problem becomes even more complicated. Now we find the phosphate and sulphate concentration in the plasma rising, while at the same time there is an excessive loss of sodium in the urine, due, we suppose, to a defective reabsorption of sodium ions from the glomerular filtrate by the remaining tubule cells. We know about the sodium loss, but this may be only one of many losses. If that is so we cannot expect to make good the deficiency simply by giving the patient more sodium chloride. Perhaps under these conditions there may be losses not only of sodium, potassium, calcium, and magnesium, but also of other elements, as for instance, manganese, that are present in very low concentrations in the body but are nonetheless essential. On all such points we are wholly ignorant, but that need not stop us from doing something to prevent deficiencies that may not even exist. So, quite blindly, we give these patients a mixture of all the ions that exist in the plasma, with the exception of the phosphate and sulphate ions. They take it as a powder dissolved in fruit juices. It is mainly salts of citric acid, which will be converted into carbon dioxide and water, leaving the bases available for use in the proportions in which they occur in the plasma.

[3] Whether an edematous patient on a low sodium intake should drink more water than he wants is a question that might be answered by each patient. Only a few observations have so far been made by them, but they indicate that a doubling of their usual fluid intake induces some increase in body weight and no proportionate increase in urine volume. These observations refer only to the immediate effect of water consumption.

Clinical Methods for Detection of Dietary Deficiencies

In all this enterprise we are thus surrounded by a great cloud of known and unknown dangers. We cannot, in out-patient or office work, get experts in vitamin and mineral metabolism to show us our errors. They have more important work to do. We are therefore obliged to get all we can from the simple clinical observations and measurements we ourselves can make. One means that we have—though it gives us only vague intimations of a possible deficiency—is to listen attentively to the patient's account of any general sense of physical lack, any feeling of weakness or discomfort that is not readily explained in terms of recognizable physical abnormality. All we get from this listening is a question, but it has its value if it leads to a review of dietary details. The other means we have is objective and very simple. The patient's body weight is recorded at each visit. If his caloric intake is adequate and yet he loses weight, we always think first of a dietary deficiency. This we learned from observing our rats We believe it is as true for our patients as for our rats that an inadequate protein consumption will always lead to loss of weight, and since this is the danger that we most fear we never fail to question body weight changes not due to inadequate calories or fluctuations in edema.

Initial Dietary Survey

In this sort of dietetic work we are, as a rule, undertaking to change the patient's customary pattern of food selection, both qualitatively and quantitatively, not over any short or limited time, but sometimes for all his life. For the patient this is a very serious matter, and so we have to begin by listening to him At the beginning this is quite obviously necessary, though all the way and to the very end we shall have to pay attention to his feelings and desires. It is necessary because, unless we listen, we are likely to tell him to do something he cannot or will not do, and then, of course, we cannot even start. So we begin by asking him questions about the sort and quantity of foods he takes. His answers are written down as a list of foods, with their approximate amounts, and their protein, calory, and vitamin content. In certain patients the sodium and other mineral constituents are added. The compilation of this diet survey begins the education of the patient. He is given the list of food values. If he says that for breakfast he usually takes half a grapefruit, an egg, a slice of toast, and a cup of coffee, he is asked to look at the list and find the grams of protein, the number of calories, and sometimes the amount of sodium in these food quantities. He is then asked how much sugar and cream he takes in his

coffee and how much butter he puts on his toast. The dietitian has before her, as the patient answers, a list of the vitamin content of various foods, and as the patient answers she can add these values.[4] When the foods taken during an average day are all set down, the total protein, calory, and other values are added and the survey is complete.

This initial survey is one of the indispensable foundations of dietetic treatment, but it is not the only one. The final decision must be a group decision in which the patient, the laboratory worker, and the doctor as well as the dietitian must be heard, since each has something essential to contribute. The doctor has reached at least a provisional diagnosis based on the history and physical examination and on his inferences as to the nature and extent of the renal lesion, and he, like the others, has a general idea as to the diet he would like the patient to take. But what has to be done is nothing general. For instance, the doctor may want to give a diet containing 40 gm of protein; but he has been shown a centrifuge tube that contains a good deal of urinary protein. The laboratory worker knows how much this is in grams of protein lost per 24 hr. Whatever this quantity is, it represents a loss that has to be made good by adding it to the 40 gm that represents the possibly ideal requirement for this patient. The dietitian has her own firsthand knowledge of the patient's food habits. Her survey is an account of the patient's food preferences; it reflects his national peculiarities and is a measure of his economic limitations. All these factors have to be taken into consideration in devising a diet that the patient can and will take. The diet will be only a quantitative modification of the food the patient spontaneously takes, and the more closely it can be made to conform with what the patient wants, the better.

This sort of work cannot be done if the dietitian is in one room, the doctor and the patient in another, and the laboratory worker is segregated in a special laboratory. Physical separation ends in mental separation. Everyone should be working together in one room so that the laboratory worker can talk to the patient and the doctor has only to look up to see the patient's collection of urine and take in its volume and color, and the dietitian can glance at the hematocrit and the urine protein tube. This physical contiguity is an indispensable prerequisite for the growth of a group that works as a unit, not simply a unit in the sense that the work of each member is related and is derived from the work of each other member, but a unit in the sense that all members are working simultaneously and together on the same problem, so that as soon as a result is obtained by one worker it at once becomes visible

[4] A convenient list is Bowes, A. de P., and Church, C. F., *Food Values of Portions Commonly Used*, 5th ed. Philadelphia, The Philadelphia Child Health Society, 1944. Price $1.50.

or can be made known to all the others, changing, modifying, or casting a new light on what each worker is doing.

PHYSICAL EQUIPMENT NEEDED

When all the results are in and the decision as to the diet to be recommended has been reached, the dietition and the patient sit down together to work out a detailed plan. The material requirements are very simple. Measurements are made with the standard measuring cup and standard spoons that are in every kitchen or can be bought in any hardware store. Calculations are made from the data listed in a book which is given to the patient and which we reproduce in the Appendix. It contains values for the protein, calory, and sodium (expressed as NaCl) contents of various foods, but in a simpler form than is usually employed. The data refer to cooked or ready-to-serve foods so that the patient is not required to allow for the losses or concentrations that may occur in cooking. Every quantity refers to the "ordinary serving" which is the amount of each food he will probably want to eat. All measurements are in terms of round numbers of standard spoonful or parts of the standard cup. The arithmetic is made easy because fractions have been eliminated, a simplification that seems allowable in view of the considerable geographic and seasonal variation in the protein and calory content of many foods. The list has been kept short, and the values given are few so that the patient may not be dismayed by the apparent complexity of his task.

With these tables the patient and the dietitian work out together a sample 24-hr diet that contains the requisite number of grams of protein, and all that has been suggested in relation to vitamins, calcium, phosphorus, and sodium. The caloric needs are given by the survey, though here, too, modification may be needed. Care is taken to show the patient that this is only one possibility and that he can get the same result in many ways and with a wide variety of foods. There are, however, many difficulties that have to be overcome. With most men the active co-operation of a wife, a sister, or a mother must be obtained and, of course, with children the mother is always necessary. But the patient must understand and do some of the work. Only comprehension ensures continuance.

METHODS FOR DIETETIC CONTROL

When the patient comes back for his second visit he brings with him a tabulation of the foods he has eaten with the total daily quantities of protein and calories he has taken. The dietitian goes over these lists carefully, correcting arithmetical errors or mistakes in calculation, and

CHAPTER 3

INFERENCES AS TO THE NATURE OF THE RENAL LESION

The methods given in Chapter 2 are practical tools designed to help us to answer two main questions: first, what is the nature of the renal lesion; and second, what is its extent? But the answers we get from the use of such methods are always indirect. They do not show us the diseased kidney itself. They reveal only certain effects produced by the disease on the urine and blood that flow through the kidney. What we actually see is material from which inferences as to the nature and extent of the lesion may possibly be derived. Any process of inference will inevitably be associated with error, and so it is proper that we should consider which results warrant some degree of assurance and which provide us with information of such an ambiguous nature that we should use it as a basis for framing a hypothesis rather than as a datum for drawing a conclusion. The error and doubt refer, of course, to the use of the results of the methods in answering the two main questions with which we are concerned. In actual work the final answers to these questions are not reached immediately from what we observe but only through a process of posing and solving many preliminary and subsidiary questions, and by taking into consideration many other facts. All observations answer some question with clarity and decision, but some bring us a long way toward our goal and others advance us only a little. In this section we shall consider what inferences may be drawn from the results of the methods designed to bring us to a decision as to the nature of the renal lesion.

CASTS

In the case of casts, as is true of all that we see in the urine, our capacity to draw valid inferences depends a great deal on our ability to reconstruct the history of what we see. The degree to which casts bear the imprint of the disease in the kidney is determined by the material from which they are made, by the place within the tubule at which they are formed, and by the changes they have undergone as they move from the kidney to the counting chamber on the stage of the microscope. But, first of all, we can be sure that casts come from the kidney.

Their cylindrical structure shows they have formed within the tubule and have been molded to the shape of its lumen. This means that we can tell from the breadth of a cast whether it has been made in the nephron or in the lower reaches of the collecting tubule system, the forest of trees whose trunks are the tubules of Bellini in the papillæ, and whose terminal twigs reach to the surface of the kidney. The internal diameter of this system, unlike that of the tubules of the nephron system, which remains approximately constant all the way, progressively widens as its termination is approached. Thus, when we see casts five or six times broader than usual we can be sure they come from well down in the collecting tubules. For the same reason, when we see hyaline casts several times narrower than usual we can suppose they come from nephrons whose lumen has been almost obliterated by a swelling of its cells.

There are physiological reasons that make it seem improbable that casts, at least such as are washed out of the tubules by the urine, are often formed near the glomerular end of the nephron. The rate of flow from the normal glomerulus into the upper end of the nephron is 100 times greater than the rate of flow into the collecting tubule at the other end. This means that the material from which the cast is formed is present in very dilute concentration in the upper part of the tubule. It does not seem probable that a solid cast will form until its constituent molecules have come closer together through the concentration of the filtrate by the tubule cells. This physiological presumption is strengthened by the observation of pathologists that casts begin to be seen in the distal tubule and in the collecting tubules but are not usually found in the proximal tubule of the nephron.

There are only two sorts of casts, if we classify them by their physical and chemical properties, but if we think of their mode of origin, there are three sorts—hyaline, epithelial, and blood casts. Hyaline casts and their derivatives dissolve in water. Epithelial casts and their derivatives and blood-casts do not.

If we take a urine that contains considerable numbers of hyaline casts and, after allowing it to stand for an hour or so, pipette out 60 cc from the bottom of the bottle and put it into four 15-cc centrifuge tubes, we have collected all the casts present in that specimen. After centrifuging for a few minutes and pipetting off the supernatant fluids, we can transfer all the casts to one tube. When we look at this material under the microscope, we see a rich network of transparent hyaline casts, but they are not pure hyaline casts because between them lie all the cells of the urine and very often epithelial, granular, fatty, and waxy casts. If, now, all this sediment is dispersed in a little water, a drop or two of dilute ammonia

solution added, and the sediment again centrifuged out and inspected, it will be found that the hyaline casts have dissolved; only the other casts and the cells remain. If we pipette off the supernatant fluid we shall have a solution of hyaline casts free from the cells and casts that are insoluble. If the dissolved material of which the hyaline casts were composed is sufficiently concentrated, and we add salt to make the concentration 0.5% or more and acetic acid until the *p*H is 5 or less, we shall find that what happened in the tubules when the hyaline casts were formed *will happen again in the centrifuge tube. As the reaction changes* from alkaline to acid there is a sudden gelling of the fluid, and the tube is now full of a transparent mold that is a cast of its lumen. This is the pure hyaline cast without visible structure or content. But it is obvious that if, before putting in the acid, we had added red blood-cells, epithelial cells, cell granules, or fat droplets to the solution, they would have been caught as they floated in the fluid when the gel formed and we should have found them embedded within the cast. Thus there are as many variations of hyaline casts as there are differences in the content of the *fluid in the tubule at the moment the casts were formed.*[1]

From the inspection of hyaline casts we may derive direct inferences as to the nature of the renal lesion. *If we find red cells embedded within* these casts we know with certainty that we have to do with some sort of disease that is associated with the passage of red cells into the glomerular filtrate. The fact that these red cells come to us embalmed within this gel is convincing evidence that at least these particular red cells cannot be derived from the mucous membrane of the urinary tract. So also with the tubule cells or cell granules and the fat droplets. These cells, or cellular derivatives, come certainly from the tubules and are direct evidence of tubule cell death and degeneration.

Epithelial casts and their derivatives also have their history, though we cannot reproduce it. The pure epithelial cast is formed by the con-

... solution
ICL,
was
made
uric
it seem likely that hyaline casts were a combination of protein ... acid which is stated by Morner to be a normal urinary *constituent.* Dr E. M. MacKay prepared some hyaline cast material from the urine of our patients who had high rates of excretion of this type of cast. Dr. P. A. Levene was kind enough to subject Dr. MacKay's preparation to an elementary analysis and found $C = 48.6\%$, $H = 2.4\%$, and $N = 11.3\%$. There was also 2.6% of S. A definitive demonstration that this material contained *chondroitin-sulphuric* acid could not be obtained for lack of sufficient material to allow the identification of the nature of the sugar. But though the precise constitution of hyaline casts thus remains undecided, it would seem reasonable to conclude that hyaline casts are formed by a *combination of protein* with a sulphur containing polysaccharide. It ... did not find any
... be prepared from

glomeration of desquamated tubule cells. Sometimes these casts are clearly divided longitudinally and are composed of two layers of cells sticking together; then it is probable that there has been a mass cell death in a certain section of a tubule, and we are looking at two semi-circles of tubule cells gummed together. Usually, however, epithelial casts have no structure reminiscent of a tube and are presumably formed from cells, desquamated at many different levels of the nephron, that have come to adhere together as the filtrate concentrates. Very often these cells are beginning to melt together so that the original cell outlines are only here and there distinguishable, and most of the cells have broken up into cell granules. Thus, by insensible gradation, we reach the pure granular cast. But this is not the end There are granular casts in which part of the granule structure has given place to a purely homogeneous refractile substance and so again, through many steps, until we reach the typical waxy cast.

This progression from epithelial to granular to waxy is doubtless a process that requires time. The waxy cast is the one that has remained within the tubule for the longest time. It is the cast that usually predominates in the first urine obtained from patients with tubule degeneration after a period of anuria, because in such cases all the casts have been delayed in their passage down the tubules. The anuria or pronounced oliguria, however, need not be general; it may be localized in certain nephrons or groups of nephrons. In that case we may find in the same urine all three varieties of epithelial casts.

The change from epithelial to granular to waxy is a consequence of the autolysis of tubule cells in the fluid within the tubule and in the urine in the bladder. This occurs after the cells are dead and have been loosened from the tubule basement membrane. It does not represent a degenerative process in the still living cells of the nephron. We therefore must not suppose that granular tubule cells or casts indicate a granular degeneration of the kidney, still less may we suppose that waxy casts come from waxy kidneys. But there is one abnormality we see in the casts and cells of the urine that is an indication that the same degeneration or infiltration must exist within the kidney. Fat droplets in a tubule cell are not the result of any autolysis of the cell, and they are not produced by the action of digestive ferments in the urine. These fat droplets existed in the cell before it died and before it floated off from the basement membrane into the stream flowing down the tubule. Even if the walls of the cells have disappeared and we are left with a cast composed, apparently, solely of fat droplets, we may take such casts as direct evidence of a renal lesion characterized by a process of fatty accumulation within the tubule cells.

Renal failure casts (8) are epithelial casts and they may thus be either epithelial, granular, or waxy. They are from two to six times broader than ordinary epithelial casts. We suppose they are formed in the collecting tubule system, not only because their diameter is greater than that of the tubules, but because after death the pathologist can sometimes show them to us as they are in process of formation within the lower reaches of the collecting tubule system. They are epithelial and not hyaline because the urine of the patients in whose sediments they are found is so watery that hyaline casts could not remain undissolved unless the urine were extremely acid. The clinical importance of renal failure casts lies in the fact that, when we see a sediment in which all the casts are broad, we know with relative certainty that the patient is uremic. We may sometimes even venture an opinion as to the degree of uremia, for, as we watch patients in whom the blood urea concentration is rising, we find that the casts tend to become broader and broader. We interpret this to mean that a gradually decreasing stream of urine due to loss of more and more nephrons permits the casts to form within the larger and larger branches that run into the trunks of the trees of which the collecting tubule system is composed.

On the other hand, just because renal failure casts are formed within the collecting tubules, we cannot derive from them any direct information about disease in the nephrons. No doubt they contain cells from still-functioning nephrons that drain into the tubules where they form, but we cannot distinguish them from the desquamated cells of the collecting tubules themselves. Certainly the finding of renal failure casts does not tell us what sort of lesion is present. They are seen most frequently in the terminal stage of glomerular nephritis, but they are to be found also in the urine of patients with renal arteriosclerosis who are uremic, or even in a lesion as completely diverse from glomerular nephritis as that found in the last stage of the development of polycystic kidneys. They do not even necessarily indicate any definite structural disease, for they can be seen in the first urine excreted after a transient anuria due to stone. The one necessary requirement appears to be that the flow of urine from the nephrons be greatly reduced. However, this reduction need not affect all the nephrons. If, through some local disease, the flow from one section of the kidneys were curtailed, we should have the possibility of the formation of renal failure casts. It seems likely that this occurs, for it is not unsual to see sediments in which only a small proportion of the casts are broad. It is only when almost all of the casts are more or less broad that renal failure casts are associated with uremia. It is also true that in many uremic patients no broad casts, no casts of any sort, are to be found. We may sup-

pose that in such cases the renal lesion is likely to be diffuse so that there are no particular sections of the collecting tubule system that get much less urine than others. An important accessory factor is the amount of fluids the patients are given. The sediments richest in the broadest casts are usually seen in uremic patients who have become dehydrated through vomiting, and so there is a sense in which this type of sediment has therapeutic as well as diagnostic significance.

Blood-casts are clots of blood. They are found in the urine of patients in whom there is an inflammatory lesion in the glomerulus. Apparently it is only when there is an inflammation involving the tuft that any appreciable number of fibrinogen molecules pass through the endothelial lining of the glomerular capillaries and through the basement membrane, and, entering Bowman's capsule, flow with the filtrate into the tubule. Within the tubule, fibrinogen is turned to fibrin. In the fluid within the tubule there is kinase derived from disintegrating cells and there is ionized calcium that has been filtered from the plasma. As the fibrils of fibrin form they entangle within their meshes whatever cells exist in the fluid. These are predominantly red blood-cells because when there is glomerulitis there is bleeding. But before the cast is excreted the red cells are usually no longer recognizable as such, for they have melted into conglomerations. The blood cast most commonly seen is, therefore, a cylindrical structure composed of ill-defined lumps whose unique characteristic is their yellow to orange color.

RED BLOOD-CELLS

A night urine of 500 cc that contains 1,000,000,000 red cells will look brown if it is acid, and it will have the color of blood if it is neutral or alkaline. We are apt to suppose when we look at it that the patient is losing a lot of blood. This is not the case. There is only a drop or two of blood; to be precise, 0 2 cc. When the quantity is of the order of tens of millions of red cells lost per 24 hr there is no perceptible effect on the color of the urine. This is an amount so minute that even though such a hematuria were to continue for decades, as it often does, it could scarcely be considered a factor in the development of anemia.

Red cells in the urinary sediment may come from any part of the urinary tract as well as from the kidney. But the red cells that started on their voyage to the outside world from the capillaries of the glomerular tuft have come a long way, have been exposed to many environmental changes, and bear the marks of their journey. In Bowman's capsule they floated in a fluid that is the plasma freed from most of its protein, and there they were still more or less at home. As they passed into the proximal tubule their environment became progressively more

discrepancy might be plausibly explained as being a consequence of the size and shape of albumin, globulin, and fibrinogen molecules and the physical characteristics of the glomerular membrane. If we think of this membrane as containing pores whose diameters are a little greater than the diameters of serum proteins and believe that in the flowing plasma all the protein molecules are chaotically arranged, we could understand that there would be little chance of the long, fibrinogen molecules hitting end on and passing through the membrane, and a much better chance of the relatively short albumin molecules getting through into the glomerular filtrate, and thus into the urine.

There is good experimental and factual evidence for each one of these statements we have made about proteinuria. Taken together, they can be made into some sort of a theory of proteinuria—one that is consistent with iself and does not contradict any well-established physiological or anatomical facts. Nevertheless, the moment we try to use it in our work we run head on into a clinical contradiction.

When we see protein in a patient's urine we know it comes from the glomerulus. We will then go on to think of the glomerular membrane and suppose that the greater the damage to the membrane the greater will be the proteinuria. This will remind us of our clinical observations as to the situations in which we find evidence in the urine of damage to the glomerulus. In the initial stage of glomerular nephritis we see the many red blood-cells that we say have come from the glomerulus, and the blood-casts that we suppose are blood clots and that we take as evidence of the passage of fibrinogen molecules into the urine. These must surely be regarded as rather direct evidence of a breaking down of the membrane that separates the blood from the glomerular filtrate. If we are skeptical about our clinical inferences we still cannot forget that the pathologists can show us the red cells, the fibrin, and the coagulated protein in Bowman's capsule. It is at this stage in this disease, when the damage to the glomerular membrane is maximal, that the theory leads us to expect the highest rates of protein excretion. But the clinical fact is that under these conditions the protein excretion rate is not high; that it does not, on the average, exceed 2 gm a day.

The patients in whose urine the highest rates of protein excretion are found are precisely those in whom the pathologists often find it hard to demonstrate more than minimal glomerular lesions, whereas both clini- [illegible] tubules [illegible] uld be most pronounced when there is the greatest [illegible] whereas clinical experience proves that the most extreme proteinurias are associated with degenerations or infiltrations of the tubule cells.

The contradiction is resolved when we recognize that the protein in the urine is only a part of all the protein that has passed the glomerular filter; that part, to be precise, that has escaped reabsorption on its way down the nephron. In this way clinical experience is validated; the immediate reason for massive proteinuria is a decrease of protein reabsorption associated with damage to the tubule cells. The experimental evidence for the glomerular origin of all urine protein still stands; there is no reason to doubt the inferences drawn from the facts we have summarized. The theory of proteinuria must be extended, however, to include the equally valid experimental facts that reveal the process of protein reabsorption by the cells of the proximal tubule.

When A. N. Richards and his group at last succeeded in drawing fluid through a minute cannula from Bowman's space, they broke through what for a century had been an entrenched line of academic warfare. They won through into an open field where decisions were reached by the outcome of an increasing and universally accredited array of experimentally determined facts. The first, and, for that time, the all-important result, was that what had hitherto been only the hypothesis of glomerular filtration became a theory supported by direct observation—a securely held key point for the future advance of knowledge.

However, the amount of fluid that can be obtained from the glomerular space in a frog is, of course, extremely small, and it was only after ingenious micromethods had been devised that it was proved that this fluid contained the concentrations of urea, uric acid, inorganic phosphate, creatinine, chloride, and dextrose observed in a filtrate of frog's plasma. Since tests for protein in the glomerular fluid gave negative results, it was quite properly described as a protein-free filtrate of the plasma. This is the origin of the belief, still quite generally held, that the glomerular filtrate contains no protein at all unless the glomerular membrane has been damaged. Nevertheless, as we shall see, this is today an unwarranted belief.

The method used for revealing the presence of protein in glomerular fluid could not consistently show the existence of any protein unless the concentration was more than 30 mgm of protein per 100 cc. In four undiluted fluids from frogs, two showed the presence of low protein concentrations, and in the other two, negative results were obtained (10). In 1941, when glomerular filtrate from six guinea pigs was obtained, two were negative, i.e., certainly contained less than 30 mgm per 100 cc, two contained between 150 and 200 mgm, and two contained amounts estimated at 800 mgm per 100 cc. These higher concentrations may well have been due to traumata. What is demonstrated clearly is that glomerular filtrate contains, at most, very low protein concentrations (11) and

CHAPTER 4

INFERENCES AS TO THE EXTENT OF THE RENAL LESION

We know what we mean when we speak of the extent of the pulmonary lesion in tuberculosis. It implies that we have seen a picture of the organ as a whole and have been able to distinguish the part that has been destroyed by disease from the part that is still functionally effective. We should like to be able to do this for the kidney. There are occasions when it seems that we are able to do just that, as, for instance, when we look at the films taken after diodrast has been given, and find only one rather large kidney with normal calyces and ureter. In most of our patients, however, disease is bilateral and diffuse, and not all of the nephrons involved are wholly destroyed, as they are by tuberculosis and cancer. In all such cases we have to use an indirect method. We have to estimate, by finding what the kidney can do, what is the amount of renal tissue still effectively functioning. This is far more difficult with the kidney than with the lung. The lung has one function; the kidney has many. Which function shall we take?

We can say we shall select the function that has the most constant relation to the total amount of effectively working renal tissue. But we shall have to remember that the structure of the kidney is just as complicated as its function. The nephron is not one but many structures. There is the structure of the filtering glomerulus and, in the tubule, there are reabsorbing structures, secreting structures, and structures concerned with the synthesis of chemical compounds. The more we learn, the more extraordinarily multiple do the structures *as well* as the functions of the tubule appear to be. So the structural quantity on which we want to base our estimate of *the extent of a renal lesion*, this "total amount of effectively functioning renal tissue," is nothing simple or easy to define.

We can, of course, take some measure of the whole kidney—its *weight*, or its *protein content*—and call this complexity, this mixture of glomeruli, tubules, vessels, nerves, and fibrous tissue, the effectively *functioning renal tissue*, since all these various structures are working together as one unit. Then we can cut off a quarter, a half, or three-quarters of this total renal mass and observe what effect that has on

different measures of renal function. The functional measure that decreases in most direct correspondence with the loss of renal tissue will be the best for us. This is the plan we have followed. We are well aware that it is naive and crude, and that the results will not interest either anatomists or physiologists. But we can hope they may be of use to clinicians who, for therapeutic purposes, must have some index of the total amount of effective renal tissue their patients possess.

THE GENERAL NATURE AND NECESSARY LIMITATIONS OF CLINICAL METHODS FOR ESTIMATING THE EXTENT OF A RENAL LESION

At the beginning of this century, when clinical investigators were measuring the rates of excretion of various substances in the urine, they were animated by the hope that they could use the results as means for the separation of patients whose renal disease was primarily glomerular in location from those in whom it was predominantly tubular. That hope was frustrated, and this whole era of endeavor was summed up by Schlayer when, in 1914, he said, *Zwischen der Schadigung der Niere und ihrer Arbeitsweise kein unbedingter Zusammenhang besteht* (17.)

Today, and with incomparably finer tools, this question can be raised again, for Homer W. Smith and his collaborators have developed methods for the measurement of both the rate of glomerular filtration and the total mass of tubules. These are great advances for physiology, but we may still be skeptical and hesitant about using them to distinguish between glomerular and tubular disease, and not alone on account of our past failures. We have a better reason for doubt based on our growing knowledge of what Ekehorn calls the "integration" of renal function (18), indicating by that term the highly co-ordinated reciprocal relations between glomerular and tubular function. The still more complex relations that arise when the structure of the glomeruli and especially of the tubules are grossly distorted by disease have been demonstrated by Jean Oliver (19). So, for the time being at least, it would seem to be a reasonable tactic for clinicians to lower their sights and be content to use functional methods, not for a differential analysis of renal structure, but in order to reach a conclusion as to the over-all quantity of renal tissue through which function is effected. That is a less difficult and ambitious program and is the only one we shall attempt.

This means that we shall not deal with a great many functional tests that reveal what Schlayer called the *Arbeitsweise* of the kidney; not even with such modern equivalents as Mosenthal's test or Volhard's dilution and concentration tests. Interest in these tests lies in their demonstration of the capacity of the kidney to alter the rates of excretion of various urinary constituents when its environment is changed. Variability is

what is measured, and the sign of disease is a *decrease in variability*. But this is a purely functional manifestation and such tests came to be developed because, at that time, there was no longer hope of finding a *direct* relation between function and structure. Attention therefore turned to function alone, under the motto, common in the German literature of thirty years ago, that it was more important for clinicians to find what the kidney could do than to know what it looked like.

There is some truth in that statement, but it is not the truth we happen to be interested in at this moment. The variability of function on which these tests concentrate is what we want to avoid. We seek a constant—a measure that will remain the same as long as the total working structure of the kidney remains the same and that will increase or decrease only with the growth or atrophy of that structure.

More than twenty years ago this group succeeded in developing a clinical method which was shown, experimentally, to measure the total amount of effectively functioning tissue in intact normal kidneys (20). We still use this method, but as a tool in clinical investigation, not as a day-to-day procedure. It needs a precision of measurement that costs a good deal in time and effort, both from the patient and from us. The required conditions are such as to preclude its use in patients who are edematous or whose diastolic pressure is high. It is an example of a relatively successful empirical solution of the problem of the relation between function and structure which nevertheless remains a clinical failure, because the work involved is too difficult and trying. The theoretically far-better-founded modern methods from which the total amount of renal tissue may be derived, inulin and diodrast clearances and diodrast clearances at high plasma diodrast concentrations, fall also, from a clinical point of view and for the time being, within this category, and will not be discussed in detail.

This dismissal of an extremely interesting subject in a few lines is imposed on us by the practical limitations of actual clinical work. It requires no apology that we thus by-pass so much that will be decisive for the future because the reader has available to him the exciting accounts by Professor Homer W. Smith of these discoveries of the past decade in the field of renal physiology (21).

A small and, it is to be hoped, a very temporary job remains. We have to build some sort of bridge between the new physiology and our present practice. Measurements of glomerular filtration, renal blood flow, and tubular mass are instruments of clinical investigation, not practical tools in clinical work. The physiologists have gone far ahead of us and it is not yet evident how we are to come abreast with them. But it will be done, and done by a process of changing their methods

into forms suited to our special purpose. It will be then that we shall fully comprehend what they have accomplished. In the meantime we have our immediate clinical problem. We have to find a method, one that we know must have an extreme simplicity of operation, by means of which, within known limits of error, we can predict the extent of a renal lesion.

Recent history shows that it would be hard to overemphasize the need of simplicity and rapidity of operation. Folin's methods for the determination of various substances in the blood and urine were designed for the use of doctors. They were easy methods but not simple and quick enough for us. They have proved extraordinarily fruitful in clinical investigation, but no doctor uses them. But the clearest index as to how simple a method must be before it will be used by a doctor is derived from noting what renal function methods he actually employs in his office work.

The great majority of doctors use only two methods: one, a measurement of the rate of urine excretion, and the other, an observation of the specific gravity of the urine. Now it is safe to say that the doctor does not use these measures because he has any illusion as to their intrinsic value. No measurements give less precise or more ambiguous results than the two he has selected. The urine volume excreted over any given time is a resultant of complicated and sometimes contradictory processes, though the variation observed in ambulatory patients is probably mainly due to variation in the proportion of water reabsorbed by the tubules The urine volume certainly has no relation to the rate of glomerular filtration, except in some sort of clinical disaster when it approaches the zero point. It thus becomes of critical importance in medicine only when there is no urine, or almost none, to measure, but through all its customary wide range of variation it is hard to think of any measurement that has less meaning Nevertheless, from this most unpromising measure we have learned much and are still learning. Volumes have been written by clinicians about "nocturia," "hyposthenuria," and "obligatory" and "facultative" diuresis, all empirical, all without benefit from the high priests of science, but all of clinical value, because, in this case, doctors themselves made the measurements and related them to their other clinical observations.

So also with measurements of the specific gravity of the urine. No one who started by remembering that the word "specific" means that each of the many substances dissolved in the urine has its own individual effect on the weight of a given volume of urine would ever have taken the trouble to measure the specific gravity of such an indeterminate mixture as urine (22). Yet, in spite of the physical chemists we still meas-

ure the specific gravity of the urine. And we are right. We have gradually developed what might be called a "feeling" for specific gravities because we have measured them ourselves, or at least have often watched as such measurements were being made, and we have connected them with other clinical observations. All goes well until we try to think about it, for the determination of the specific gravity of the urine is an artistic rather than a scientific procedure, though not on that account to be despised. In any case, it has the prime virtue of being our own, like urine volume measurements. *They have come to be our measurements* because they take only a few seconds of our time.

All other "tests of renal function," even such simple ones as the phenolsulfonphthalein test, are usually turned over to the "laboratory." That is why, though immensely more informative than urine volume or specific-gravity measurements, they have yielded so little of clinical value. This is true not only because the laboratory workers often work in a slipshod manner, as is not unnatural since *they never see the patient* and are practically never consulted about the clinical problem; it is true also because they often know better than the doctor how vain it would be to spend technical care on material collected and timed by those to whom the doctor delegates this sort of work.

Anyone, for instance, who has had the curiosity to watch the intramuscular administration of 1 cc of phenolsulfonphthalein to almost any patient in almost any hospital will be in a position to comprehend that the reasons for the high variability in the results of this test depend on causes simpler than the admittedly very complex series of mechanisms through which phenolsulfonphthalein is excreted. He will see a nurse taking a 1-cc syringe from boiling water while it still contains from *0.1 to 0.25 cc of water. He will see her pulling in* the dye from the ampoule until the 1-cc mark is reached, and will observe her then inject this variously diluted mixture into the patient—into muscle if he is thin, into adipose tissue if he is fat. How can we expect the laboratory worker to take a pride in the precision of his measurement when he knows that the injection has probably been given *in some such manner* as we have described and that the urine collections have been timed *in the way* nurses notoriously time urine collections? In this way, doubtless, we get "results." If we take care to evade any knowledge of detail, we may pride ourselves on our businesslike efficiency. But medicine is not a business and this mode of work disintegrates our morale and the morale of those whom we exploit. It would be better to have no measurements at all than to run the risk of being misled by such results.

The poison, of course, begets its own antidote in the form of an instinctive disinclination to use the results of such renal-function tests

in the formation of a diagnosis, unless they happen to support ideas already derived from our own direct observations. But even if the error is thus neutralized by neglect, time and effort have been wasted. Nor is it a satisfactory solution to renounce all attempt at measurement and relapse into the archaic simplicities of the past. That, of course, is easy, but it is a backward step.

The real cure is not easy. It involves organizing the nurse, the laboratory worker, and the doctor into a team in which each member has his special part but in which each also understands the significance of the enterprise as an organic whole and comprehends how all the different parts are related to one another. As far as the doctor is concerned it can never be a matter of simply coming in, ordering that a certain procedure be carried out, and walking out. Like the others, he must be in it all and see it all, not standing idly by, not critically watching every step, but getting on with his own proper job while his fellow workers get on with theirs. Thus, each worker takes in and understands what the others are doing, and all finally come to an agreement as to the meaning of what they have done together. At first this is complicated and difficult, even when the procedures are very simple and quick. But the simplicity and rapidity of the methods is not in itself an end; it is only a necessity until we get organized. We can go on from that first step; it is only a beginning.

There is a special limitation laid on clinical tests of renal function that arises because we want a method we can use at once on all our patients. If we are not willing to wait until they have complied with restrictions that exclude variable factors inherent in ordinary life, if we cannot ask them to follow instructions designed to produce extreme and unusual conditions, if we are to take them just as they are when they come to us, then we shall have to recognize that we are closing the door on many possibilities and are willing to accept less unequivocal results for the sake of general applicability—a choice no scientist would make. But it is not for us to select our subjects, we have to do the best we can for all who come—young and old, strong and weak, those who can follow complicated instructions and those who cannot.

Still another limitation is a consequence of our being obliged to have a method that will be so foolproof that each and every determination will be entirely trustworthy. In scientific work this is not necessary, and the dependability of the individual observation is sacrificed for high average precision. All sorts of complicated gadgets are devised by scientists for the purpose of getting the highest possible degree of average precision, even though, not infrequently, something goes wrong with the machinery and a large error is made. That possibility is accepted with

after birth that number is reached. Thereafter, nephrons may be lo but no new ones will ever take their place. Thus, when we take o three quarters of all the renal tissue, we can be sure that the numb of nephrons left will be no more than 25% of the original number. On the number remains steady. The size of the remaining nephrons at on begins to change, and it is the size as well as the number of nephro that determines the amount of effectively functioning renal tissue.

As a first step, therefore, we must know as accurately as possible wh is the normal amount of renal tissue. But what is "normal"? In its ge eral meaning it is certainly nothing fixed or absolute but only what usual under certain circumstances. As applied to the kidney we migh say it was the average quantity found in healthy animals of a certai standard size. Let us provisionally accept this definition so that we ma be able to see in terms of kidney weight what it means. In Table 5 w give the weight of both kidneys of rats whose body weight was 150 gn and in whom no process of a pathological nature, either general or renal was detected.

TABLE 5

KIDNEY WEIGHT IN RATS OF 150 GM BODY WEIGHT

KIDNEY WEIGHT	NO. OF RATS	SEX	FOOD
mgm			
956	90	♂	Protein free
973	90	♂	*No food for 7 days*
992	222	♀	Stock diet
1,226	90	♀	Stock + 50% casein
1,322	30	♂	High casein
1,666	11	♂	High gelatine

Long ago, when we first made such observations, we were surprised, for like most people we had thought that the size of the kidney would bear some fairly constant relation to the size of the body, in much the same way that a man's arms and legs are, in general, proportioned to his body size. We were also somewhat dismayed because it was at once evident that we should have to do much more work than we had anticipated. If what we customarily regard as normal can vary from 956 mgm to 1,666 mgm, that is, by over 74%, we have no sufficiently fixed total quantity of kidney from which certain proportions can be removed. No constant relation between structure and function can be derived if structure is such a fluctuating quantity.

It was thus necessary to undertake a systematic investigation of the dietary factors that change the kidney. It is evident from Table 5 that there was something in the various foods we gave that led to marked differences in the weight of the kidney, and it seemed probable that these foods were effective because they changed the urine. It was pos-

sible, of course, that some ingredient present in certain foods might lead to an enlargement of the kidney even though the quantity of this material excreted in the urine was small, but it seemed more likely that the effect was due to some urinary constituent whose rate of excretion was large.

Urine consists mainly of three substances—water, sodium chloride, and urea. It is easy to produce very great differences in the volume of urine and yet keep all other factors constant. When rats are given nothing but dilute dextrose solutions as food, they try to get enough calories and have to drink such enormous amounts that the weight of urine for 24 hr often exceeds their body weight. Given nothing but concentrated solutions of dextrose they drink very little and the urine volume may be only 2 or 3% of the quantity excreted when the sugar is dilute. Yet, in spite of these huge variations in water excretion, no significant difference in the weight of the kidneys is produced. Under these conditions water excretion changes are therefore not a factor. Sodium chloride can also be excluded. We have many experiments in which the rate of excretion of sodium chloride was varied over a wide range, and yet no change in the size of the kidney was produced which could be attributed directly to the salt excretion. On the other hand, when urea, as such, is added to the diet there is an increase in kidney weight which varies in degree with the amount of urea consumed.[1] We believe that the changes in kidney weight shown in Table 5 are principally due to differences in the rate of urea excretion. Food differences are effective mainly, though not entirely, insofar as they induce differences in urea excretion. This is so because any excess of protein in the food over the amount needed for maintenance and growth is followed by an increase in urea excretion by the kidney. Yet this is not the whole story, for when urea is given the kidney weight increase is definitely less than when a protein like casein is given in quantities that have the same N_2 content as the urea (21). Some of the casein effect is evidently due to other protein derivatives than urea. But the greater part of the effect of the diets enumerated in Table 5 is the consequence of the differences in the rates of urea excretion induced by their varying protein contents.

We can now return to a more complete definition of the normal amount of kidney. It is that quantity we find in healthy rats of the same body weight that have consumed the same amount of the same sort of

[1] This is not necessarily true under all circumstances. Thus when urea is taken over a major portion of the total life span of a rat there may be no enlargement of the kidneys. In 1921 a few such long term experiments showed no gross change in kidney weight but the poor condition of both control and experimental animals prevented us from drawing any definite conclusions. Hopper, however, has recently made the same observations under what appear to be more favorable conditions (personal communication). The reason is not immediately apparent.

that will give only plus or only minus errors. For example, differences in the temperature of the room will change food consumption and thus change kidney weight. When the temperature falls more food is eaten; when it rises, less. The temperature of our rat-colony room is controlled so that it never falls below 18° C, but we have no way of preventing the

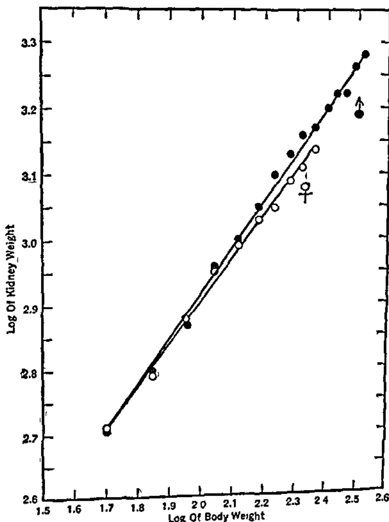


Fig 5

temperature from rising. We also have the impression that there are what we may call "social variations" in food consumption, though we have never been able to understand them. There appeared to be days on which the whole colony was disturbed and did not eat as much as usual for reasons that are not apparent to us.

For these and many other reasons we feel that prediction tables can never take the place of separate, synchronous controls for each experiment. The value of the tables is that they give us a general yardstick by which we can suspect that some special variable has been at work whenever we find deviations from the general rule greater than those that are customary.[2]

Experimental Reduction of Effectively Functioning Renal Tissue and Measurement of Remainder

If we want to remove 25% of all the kidney tissue, the rat is weighed and the expected kidney weight is read from the table. If the rat is 139 gm in weight and is female, the predicted kidney weight is 1,000 mgm. A quarter of this is 250 mgm, and this is the amount to be cut out. Under ether anesthesia one kidney is exposed by a flank incision, small bull-dog rubber-padded forceps are placed on the renal pedicle, and about one eighth of the mass is snipped off from one pole with scissors. This tissue is immediately weighed on a torsion balance to within 1 mgm. The forceps are taken off in from 10 to 15 sec after their application. There is then an oozing of blood from the wound, which clots almost at once. The incision is closed and the same procedure is carried through on the other kidney and enough is cut off to total 250 mgm. It

the objective requires. We give the coefficients of variation of kidney weight as determined from the individual variations from the predicted weights in groups of from two to eighty rats. These were controls we had used in previous experiments. They were all male rats from 90 to 110 days old that had been reared on our 17% stock diet.

RATE OF INCREASE IN THE RELIABILITY OF AVERAGE PREDICTIONS OF KIDNEY WEIGHT FROM BODY WEIGHT AS THE NUMBER OF ANIMALS FROM WHICH THE AVERAGE IS DERIVED IS INCREASED

no. of rats in each group	no. of groups	total no. of rats	range of coefficients of variations, %	average coefficient of variation for all groups, %
2	20	40	10.0 to 1.1	±5.7
5	10	50	4.8 to 2.0	±3.5
10	5	50	2.8 to 2.2	±2.6
20	3	60	2.3 to 1.7	±1.9
40	2	80	1.4 to 1.2	±1.3
80	2	160	1.0 to 1.0	±1.0

This table shows that, for this measure, maximum errors as high as those indicated by a coefficient of variation of ±10% may be incurred when only two rats are taken, and that the maximum error falls rapidly at first until with ten rats it is less than ±3% and thereafter decreases only slowly so that with twenty it is about ±2%, with 40, ±1.3 and with 80, ±1.0. These facts seem to indicate that we have sometimes wasted time and effort by taking an unnecessarily large number of rats in our control and experimental groups.

trophy of the kidney," and thus to avoid what we take to be the faults of that expression. The word "compensatory" has unfortunate teleological implications and, in addition, suggests that an adequate explanation of the phenomenon has been achieved, whereas the word "hypertrophy" is too narrow, since the process is one that includes hyperplasia as well as hypertrophy. All we really know is that when we take out part of the kidney the remaining part grows larger. No one will maintain that we know anything definite about "why," nor even very much about "how." It is the more necessary, then, to be careful about the choice of words because the process, whatever we choose to call it, is of great clinical importance. This is nature's way of making good a loss and though we, as children of nature, may sometimes do better than our parent, that ability comes only through a comprehension of her mechanisms. In this endeavor nothing is more likely to still curiosity and initiative than a nomenclature that implies knowledge where only ignorance exists. So here we prefer a purely descriptive terminology.

When one kidney is removed from a rat the remaining kidney at once begins to grow larger. This growth is very rapid at first so that 2 days after the operation about half of all the new growth that will occur has been accomplished. Thereafter, growth goes on, but more and more slowly the longer the period of time that has elapsed since the nephrectomy, until, when 40 days have gone by, growth ceases. The form of the curve of growth is given in Figure 6 and the data from which it was derived in Table 8.

TABLE 8

RATE OF RESTORATION OF KIDNEY WEIGHT AFTER UNILATERAL NEPHRECTOMY

TIME	NO. OF RAT	KIDNEY WEIGHT FOUND % OF CONTROL KIDNEY WEIGHT
Before operation	276	100 0
At operation		50 0
2 days after operation	274	63 0
5 days after operation	486	66 8
10 days after operation	428	70 8
20 days after operation	334	73 3
40 days after operation	312	74.3

When one kidney and half of the other kidney are removed, the remaining quarter of a kidney grows very rapidly at first, so that 5 days after the operation the protein it contains has almost doubled. Thereafter, the rate of growth decreases, but 40 days later it is still growing, and growth continues for at least 80 days. In this case, for the reason already given, growth was measured not by weight but in terms of total protein content. The curve of growth is given in Figure 7 and the data in Table 9.

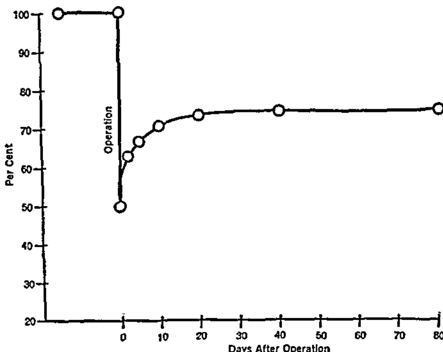


Fig. 6. Rate of restoration of kidney weight after unilateral nephrectomy. Equal [illegible]

stock diet before and after the operation. They were either 30 or 70 days old on the day of operation. The absolute kidney weights are given (along with other data) in a paper by Addis, T. and Lew, W. in the *Journal of Experimental Medicine*, 71:325, 1940. The extension of the line from 40 to 80 days is not based on observations made during this experiment but is justified by other experiments in which, after correction for body weight variation, no significant difference was found in the weight of the kidney 40, 60, and 120 days after unilateral nephrectomy.

TABLE 9

RATE OF RESTORATION OF KIDNEY PROTEIN AFTER 75% REMOVAL

TIME	NO OF RATS	KIDNEY PROTEIN AS % OF ORIGINAL TOTAL KIDNEY PROTEIN	PROTEIN LEFT AT OPERATION MGM	PROTEIN FOUND AT KILL MGM	PROTEIN RESTORED MGM
Before operation	276	100 0	161.6	161.6	0 0
At operation	276	25 0	40 4		
5 days after operation	43	46 5	40 4	75 1	34 7
40 days after operation	72	58 3	40 4	94 2	53 8
80 days after operation	96	66 8	40 4	107.9	67.5

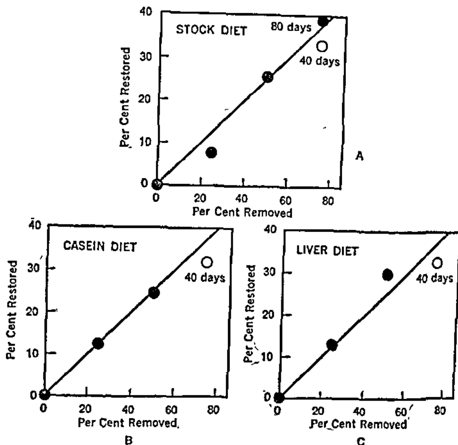


Fig. 8. Relation between the amount of kidney protein removed at operation and the amount of kidney protein finally restored. These determinations were made 40 days after operation. This is an insufficient time for full restoration after 75% of the total protein is removed, and the open circles which represent the quantities 40 days after 75% removal fall below the line, whereas the only observation (filled-in circle) made 80 days later obeys the rule that about half of the quantity removed is restored.

When we reduce the kidney to 25% of its original size we reduce the number of nephrons to a quarter, that is, from 61,600 to 15,400. From that time on there will be no more than 15,400, since new nephrons are never formed. We can think of it even more simply and suppose there were originally four large nephrons. After the operation there is only one. So when we find that a quarter of the whole kidney contains 39 4 mgm of protein and that after 80 days it has grown until it contains 99 7 mgm of protein, we can imagine that single nephron growing until it is 2 ½ times bigger than it was before. This, of course, is only approximately true, because the total protein content we measure includes the protein of the connective tissue, vessels, nerves, and the collecting tubule system as well as the protein of the nephron. It is, nevertheless, substan-

tially correct, since the great bulk of the kidney protein is nephron protein.

Now the question arises as to whether the enlarged nephron is just like an ordinary nephron, except that it is bigger, or is it, perhaps, asymmetrical—a distorted nephron in which some parts are magnified out of proportion to other parts? The answer is given in a functional and structural study of the nephron of the rabbit before and after unilateral nephrectomy we carried out in collaboration with Jean Oliver in 1924. The increase is asymmetrical. Dr. Oliver found that the proximal convoluted tubule enlarges out of all proportion to the other parts of the nephron[a] This is more than a curious anatomical fact; it has meaning in relation to function; it has clinical significance since in his recent book *The Architecture of the Kidney in Chronic Bright's Disease*, Oliver has beautifully and precisely demonstrated this most revealing structural change in the remaining nephrons of patients whose total nephron number had been greatly reduced in the course of glomerular nephritis; and it is a fact we must keep in mind when we try to interpret the results of the experiments we are now describing. In this last relation it means that the kidneys whose protein content we finally measure at varying intervals of time after cutting out part of the renal tissue are new kidneys, qualitatively different, and therefore not directly comparable with the kidney we had to deal with before the operation. By the laborious device of measuring protein content we escape certain errors involved in trusting to kidney weight, only to find that we have on our hands a series of structurally altered kidneys, each of which contains an increasing proportion of specifically working tissue the more we have reduced the size. This is an example of a special difficulty in biological, as opposed to physical, measurement. At least on the average, atoms and molecules are steady, dependable structures, but a kidney changes its constitution even while we are looking at it. There are no biological constants; there is no possibility of isolating one part from the ever-changing relationships between the parts that make one whole.

In Figure 9 we give an illustration of this lack of proportion in the growth of the various parts of the nephron when the number of nephrons

[a] In addition to this predominant lengthening and thickening of the proximal tubule, there is a very definite enlargement of the glomerulus. We shall later give the evidence for the view that the increase in proximal tubule size is an example of "work hypertrophy." But the glomerulus, as far as we know, does no work. The energy for filtration is provided by the heart Glomerular enlargement must, therefore, be induced by some other mechanism. Since Roy Cohn has given experimental proof that the increase in tissue in the remaining lung after unilateral pneumonectomy is initiated by the stretching of the tissue (30), it is reasonable to suppose that this glomerular increase in size is associated with the stretching of the tissues of the capillaries and of Bowman's capsule that follows the increased flow of blood and the increased filtration associated with the great increase in size of the proximal tubule.

is reduced or when the protein content of the diet is increased. We are indebted to Jean Oliver for the drawings of the three pairs of nephrons he dissected out from the kidneys of three rats, all of them 110 days of age, which we sent to him after they had been subjected to such change of conditions as have been dealt with in this chapter.

The nephrons shown in part *A* had a proximal tubule volume of 0.022 cu mm. Their glomeruli are attached to a twig of the arterial tree on which a few glomeruli detached from their tubules still hang. The periglomerular convolutions of the proximal tubule and its descending portion are *black*, and the ascending limb of Henle's loop and the second convoluted tubule are left in outline. These represent nephrons from rats on our stock diet.

The next drawing (*B*) shows the increase in nephron size that occurred 20 days after an operation in which the total number of nephrons had been reduced to a quarter of their original number, but all other conditions were kept constant. There is an enlargement of the whole nephron, but it can be shown that the degree of increase is greater for the proximal tubule than for any other part. In the last drawing (*C*), another factor making for renal hypertrophy was added by giving a diet adequate in vitamins and minerals that contained 86% of lactalbumin. The enlargement of every part of the nephron can be seen at a glance. In one of these nephrons the second convoluted tubule can be seen entering a twig of the collection tubule system, and in this instance we can be sure that the whole nephron is seen. But the fact that is important for us is the excessive increase in the proximal tubule, the part that all evidence indicates is primarily concerned with the osmotic work of the kidney.

Urea Measurements and the Amount of Effectively Functioning Renal Tissue

Urea is the quantitatively predominant urinary constituent. It is the substance whose excretion requires much the greatest part of the total osmotic work of the kidney. It can be determined with a reasonable degree of precision. We therefore decided to find what effect a reduction of the amount of functioning renal tissue would have on the rate of excretion and concentration of urea in the urine and on the concentration of urea in the serum. These measurements were made on rats living under the ordinary conditions of their life in our rat colony. We usually worked with groups of ten rats at a time, and they were together allowed the freedom of a large cage, were subjected to no limitations relative to their total food and water consumption, and in general experienced no alteration in their usual routine up to the moment when they were anesthetized with ether and killed in order that we might obtain their

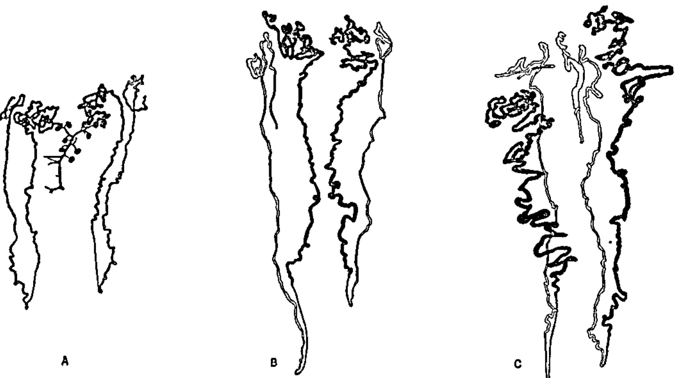


Fig 9. *A*, Control conditions. *B*, Control conditions plus reduction of nephron number. *C*, Control conditions plus reduction of nephron number plus high protein diet.

blood. This plan was followed for the reasons given in the discussion in this chapter of the need, in any clinical method for the estimation of the extent of the renal lesion, of being able to make our observations under all ordinary conditions.

METHODS

The urine was collected on large sheets of blotting paper placed nearly perpendicularly beneath a wire cage. With this arrangement the urine was adsorbed on the paper while the stools were deflected from the steeply sloping surface and fell into a receptacle below. The possibility of a bacterial decomposition of urea on the blotting paper was precluded by impregnating the paper with 1% phosphoric acid and drying it before use. Known quantities of urea in solution sprinkled on this paper were entirely recovered 24 hr later. When the period of urine collection was completed the paper was disintegrated in a known volume of water, the pulp centrifuged off, and the determinations made on the supernatant fluid. This device made it possible for us to measure the rate of urea excretion while the rats were eating. This was a considerable technical advance for us. Previously we had been unable to collect urine from rats given solid food without the urine's becoming contaminated with particles of scattered food, unless we used mechanisms that interfered with free feeding. In addition, this method enabled us to weigh the food consumed, since scattered food could be recovered. The food troughs were hung outside the cage and could not be entered by the rats, and we are confident that, with adequate washing of the wire floor, we got all the urea excreted.

When a rat is picked up and a beaker containing cotton wet with a few drops of ether is put over his nose, the bladder contracts and the urine it contains can be directly collected. When this is done at the beginning and end of a period of time we get precisely timed collections. Our rats are accustomed to being handled and this procedure does not seem to disturb them appreciably, but in this case we were anxious to avoid even the slightest deviation from ordinary conditions and in making our 24-hr collections we transferred the animals into and out of the collecting cage without emptying their bladders. At the end of the 24-hr period the urine in the bladder was collected in the manner described. The volume was often very small. It was determined by weight or, more frequently, by collection in tubes graduated at intervals of 0.01 cc. A separate determination of the urea content of this directly collected urine combined with its volume gave us the urea concentration in the urine.

It will be noted that under these circumstances the timing of the

24-hr urine collections had only an average exactitude. Since large numbers of animals were used in these experiments we may assume that the quantity of urine in the bladder when the rats were put into the collecting cage would, on the average, be equal to the quantity in the bladder 24-hr later when the urine was collected for the determination of the concentration of urea in the urine, so that the urine adsorbed on the blotting paper could be taken as representing the urine of a 24-hr period.

As soon as the bladder urine had been collected the rat was dropped into a mason jar with a screw top packed with cotton wet with ether. In less than 30 sec the animal was asleep. The abdomen was then widely opened, the gastrointestinal tract displaced to the left, the abdominal aorta snipped with scrissors, and the blood collected in a centrifuge tube. After it had coagulated, the clot was detached from the glass and the tube was centrifuged for a few minutes to separate the serum we used for the determination of the serum urea concentration. In collecting the blood care must be taken not to sever the ureters, for the concentration of urea in a rat's urine may exceed 10,000 mgm per 100 cc, whereas the concentration in the serum is usually no more than 20 to 40 mgm per 100 cc.

Urea, in both urine and serum, was determined by a urease aeration titration method that has been described in detail elsewhere (31). After collecting urine and serum urea concentrations from individual rats in sufficient number to permit the calculation of variabilities, measurements were made on the pooled urines and serums of groups of rats, there being usually ten animals in each group. The bladder urine from all the group was collected in one tube. For the serum pool, 1 cc of serum was taken from the blood of each rat.

Although we took the rats just as they were without any interference with their ordinary life, there were two aspects of these experiments in which pains were taken to obtain a quite unnatural uniformity. First, the control and experimental rats were, as far as we could contrive, identical. They were all young female rats selected so that the average body weight and distribution of weights were closely similar. As far as possible the controls were littermates of the experimental rats. In many experiments the animals were selected so that at the time they were killed the average body weight of the controls was the same as that of the experimental groups. This was done in order that we might avoid the necessity of having to make a correction for differences in body weight before comparing our results. Corrections based on body weight must always introduce some error, even when the correction is based on such an extensive series of observations as we have described earlier in this chapter. For many of the final averages we give here, this com-

plete equality was not possible, and the correction of kidney weight was made in accordance with the power equations given elsewhere (26) Since there was no great divergence in body weight, these corrections were always small, hence, we feel that no appreciable error was introduced. Second, a controlled but variable factor was introduced with the food. Urea measurements, in particular, are of course directly affected by the quantity of protein consumed, so these experiments were carried out with diets that contained different concentrations and different varieties of protein. In each case the controls and experimentals were given the same food in unlimited amounts, with all the water that was desired. All the diets were capable of supplying much more than adequate quantities of minerals and vitamins and were designed to provide variation in the consumption of various proteins.

The control groups to which we have referred were those in which the kidneys were left intact. We tried to make them in every other respect the same by subjecting them to an operation in which both kidneys were exposed and handled. From the experimental groups, 25%, 50%, and 75% of the total renal tissue was removed. At the end of the period of observation the kidneys of the control groups and the remnants of renal tissue found in the experimental groups were weighed and their protein content determined in the manner already described.

The principal results are given in graphic form by plotting the various measures of function against kidney protein. In order to facilitate comparisons between the various functional measurements they are given as percentages of the quantities found in the control rats with intact kidneys, the control values being taken as 100% and the values found in the experimental groups with various degrees of reduction in renal tissue being expressed as plus or minus percentages of the control. These percentages are plotted against the quantities of protein found in the kidney, expressed as minus percentages of the amount in the control rats taken as 100%. The continuous diagonal line in the graphs is that which would have been followed if the functional measurements had varied directly as the quantity of kidney protein. The circles are the observations, the broken line connecting them shows the relation between the measurements of function and of structure.

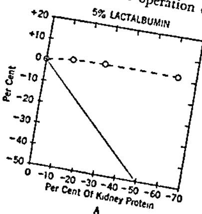
It is proper that here we should confine ourselves narrowly to the consideration of the main problem at issue, i.e., what is the most hopeful direction in which to look for a clinical method for the estimation of the extent of a renal lesion. For that purpose this method of presentation, for the most part, suffices, but we are well aware that there is much more in these data than we indicate and that other interpretations than those we give are possible. Those whose views may differ from ours and who

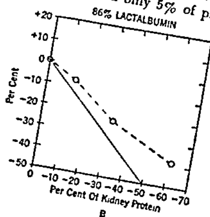
may be interested in other and wider questions than those we are concerned with in this chapter will find the actual measurements given in Chapter 8.

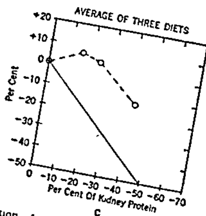
RATE OF UREA EXCRETION

The relation between the 24-hr rate of urea excretion and the quantity of kidney protein found after the removal of none, of 25%, of 50%, and of 75% of the total amount of functioning renal tissue is given in relative form in Figure 10.

Figure 10 *A* shows the results obtained when the observations were made 7 days after operation on a diet that contained only 5% of pro-







ate of urea excretion *A* shows the rate on a 5% lactalbumin diet; *B* the 86% lactalbumin diet, and *C* gives the average of rates found with three with and without protein supplements. The continuous diagonal line e relation between rate and kidney protein that would have existed if there had been a direct one to one correspondence.

tein in the form of lactalbumin but in all other respects was adequate. This graph shows that the rates remain about the same both when the kidney is intact and when it has lost more than 60% of its total mass. The conclusion must be *that nothing was learned about the extent of* the renal lesion from measuring the rate of urea excretion.

But perhaps that is only true for these particular conditions (*observations made 1 week after the operation in rats on a 5% lactalbumin diet*). What would be the result if everything else were kept the same but the concentration of lactalbumin were increased from 5% to 86%? The answer is given in Figure 10 *B*. The results show that the smaller the *kidney the smaller is the rate of urea excretion, and that a fairly good* correlation exists, though the rate does not decrease quite as much as does the kidney. The principal difference between the experiments shown in parts *A* and *B* is that in the latter the kidneys were called on to excrete much more urea. In the controls the average 24-hr rate was 78 mgm on 5% lactalbumin, whereas on 86% lactalbumin the rate had risen to 1,084 mgm per 24-hr. Is it true that even a little kidney can *excrete a little urea, but that when a large quantity of urea has to be* excreted the smaller the kidney the more incapable it becomes? This hypothesis gives a plausible explanation of the difference between parts *A* and *B*, but there is another explanation that is simpler and more direct.

The serum urea concentrations observed at the end of the 24-hr period over which the excretion of urea was measured were very different in the two experiments. The size of the kidney was reduced from 100% to approximately 87%, 70%, and 38% in both cases, but on the 5% lactalbumin diet the respective serum urea concentrations were 20 mgm%, 26 mgm%, 32 mgm% and 28 mgm%, whereas on the 86% lactabumin diet the concentrations were 70 mgm%, 91 mgm%, 134 mgm%, and 183 mgm%. With the food of high protein concentration *there was thus a steadily rising degree of uremia as the quantity of renal* tissue diminished. Uremia is a state usually associated with loss of appetite. Could it be that the rates in *B* fell because the rats ate less as they became more and more uremic? This is an idea that can be tested, for in each instance the quantity of food consumed was measured. On the 5% lactalbumin diet *the amounts eaten were not very dissimilar*, but on the 86% diet the 100% kidney rats ate 7.9 gm per rat per day; on 87% of kidney 7.17 gm; on 68%, 6 0 gm; and on 38%, 6.4 gm. The relation is not very direct and there were doubtless a multitude of other factors involved, but there is every reason to regard a declining food consumption as a major cause of the declining rates of urea *excretion*.

This general position is supported by the results of observations on *rats which* were divided into four groups of diminishing quantity of

renal tissue (Figure 10 *C*). The conditions are dissimilar because the observations were made not 1 week but 40 days after operation, and the results are a summation of observations on three diets, one with moderate and the other two with high concentrations of different proteins. Part *C* contains something of both parts *A* and *B*. It agrees with *A* in denying any direct relation between urea excretion and size of kidney. With a 24% reduction in the amount of kidney, the rate is even a little higher than in the controls. It agrees with *B* in that with the most marked reduction in kidney size there is a 14% reduction in the rate of urea excretion. In this latter case, however, the food consumption was reduced so we need look no further than that for the main reason for the fall in rate.

Perhaps the time relations are important? We have given the rates at 1 week and at 40 days after the kidney has been reduced in size. What would happen if we cut out three-quarters of the kidney and observed the rates every day from the time of operation? In this experiment we avoided the uncertainties that arise from fluctuations in urea excretion, due to variation in the quantity of protein consumed, by giving the rats no protein at all after the operation They were fed a 5% solution of dextrose in salt solution of which they all drank large volumes. The results are given in Table 11.

TABLE 11

EFFECT OF REMOVAL OF THREE-QUARTERS OF THE KIDNEY ON THE DAILY RATE OF UREA EXCRETION AS COMPARED WITH CONTROL RATS SUBJECTED TO A SHAM OPERATION*

	AVERAGE RATES OF UREA EXCRETION	
day after operation	75% kidney removed mgm per 24 hr	0% kidney removed mgm per 24 hr
1st	155	146
2nd	153	77
3rd	126	84
4th		74
5th	111	72
6th	98	62
7th	85	63

* Both groups fed on 5% dextrose in 0.4% sodium chloride from the time of operation.

The figures in Table 11 show that the kidney reduced to a quarter of the original size excretes more urea than the undiminished kidney, and this under conditions that allow us to be sure that the extra urea came from the protein of the rat and not from any protein in its food. We suppose that the removal of renal tissue was associated with an increase of what used to be called "endogenous" protein catabolism. This means that more amino acids derived from the proteins of the rats' tissues were deaminized so that more urea was formed in the experimental than in the control group.

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This general position is supported by the results of observations on rats which were divided into four groups of diminishing quantity of

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TABLE 11

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outcome on the 5% lactalbumin experiment can thus be interpreted as predominantly a result of hemodynamic changes.[5]

When an 86% lactalbumin diet was given, the hemodynamic effects had already approached their maximum throughout the whole range of variation in kidney size. As we shall show, the effect of an increasing protein consumption on glomerular filtration becomes less and less as the quantity of protein consumed increases, so that any further increase when the level of consumption is very high would presumably have a negligible effect. Relative to the size of the kidney the protein consumption in the 86% lactalbumin experiment with 75% of the kidney removed was far higher than any we can reach even if a diet of 100% protein were taken by a rat with intact kidneys. If 4 gm of protein were taken by rats whose kidneys weighed 1,000 mgm, the same consumption in rats with only 250 mgm of renal tissue would be not 4 but 16 gm of protein per gram of kidney. The form of the curve in Figure 16 on page 91 that relates the urea clearance and urea excretion (or protein consumption) suggests that long before such very high levels of relative protein consumption were reached the curve would have become asymptotic because the maximum possibilities of increased glomerular filtration through increase in rate of blood flow and intraglomerular pressure would have been approached. In that case the reduction in the extent of the filtration surface induced by the removal of glomeruli would become the predominant factor, and the progressive increase in serum urea concentration which was found would follow. In a mechanically pure experiment after time had been given for the accumulation of urea in the body we should have again found a constant rate of urea excretion with all sizes of kidney. But here a general somatic effect intervened so that, with increasing uremia, we got decreasing protein consumption and, as a consequence, that pseudo relation between size of kidney and rate of urea excretion which is shown in Figure 10 *B*.

The general conclusion must be that from the rate of urea excretion we can learn nothing about the extent of a renal lesion.

URINE UREA CONCENTRATION

In Figure 11 we give the relative changes in urine urea concentration and kidney size.

There is a curious contradiction between parts *A* and *B*. On the 5% lactalbumin diet *a reduction in kidney size* is associated with *a rise in* concentration *(A)*, whereas with 86% lactalbumin the concentration falls

[5] We do not take into consideration the possibility that under ordinary conditions only some of the glomeruli are filtering while the remainder are quiescent, because the recent evidence supports the view that glomerular intermittence is restricted to the amphibian kidney, and that in mammals all the glomeruli are always filtering.

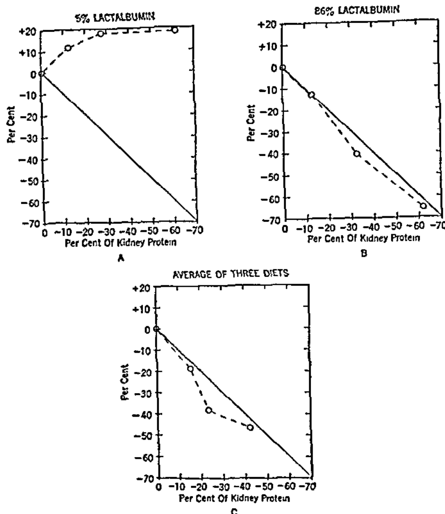


Fig 11 Urine urea concentration.

in proportion to the reduction in kidney size *(B)*. In the experiments with moderate- and high-protein diets there is also a progressive decrease in concentration, though the correspondence with the quantity of renal tissue is not so close as in *C*.

The contradiction comes about because the concentration of any substance in the urine is determined by two variable quantities, which sometimes change in opposite directions. One is the rate of excretion of the substance; the other is the rate of excretion of water. On the 5% lactalbumin diet the rate of urea excretion remained constant as the kid-

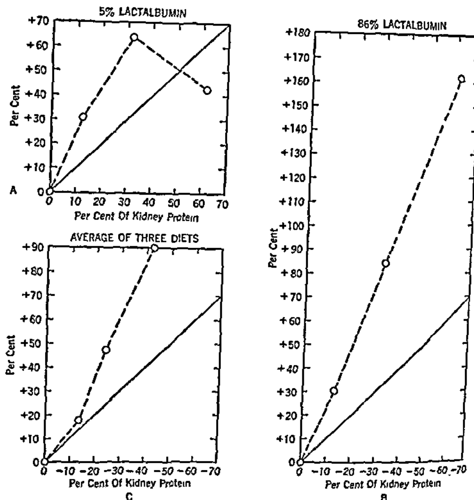


Fig 12 Serum urea concentration.

TABLE 12

SERUM UREA CONCENTRATIONS IN NORMAL RATS ON DIETS THAT INDUCED VARIATION IN PROTEIN CONSUMPTION AS MEASURED BY INCREASE IN THE RATE OF UREA EXCRETION

DIET	RATE OF UREA EXCRETION	SERUM UREA CONCENTRATION
	mgm per 24 hr	mgm per 100 cc
10% dextrose in 0 4% NaCl	26	4 2†
5% lactalbumin	78	19 8
Stock diet	347	34 9
Liver stock diet	578	44 4
Casein stock diet	1,070	67.1
86% lactalbumin	1,084	70.1

† This figure is an average taken from a series of experiments not discussed here. It is introduced in order to show the wide variation in the serum urea concentration of normal rats The average control figures from the stock, liver stock, and casein stock diets are those whose averages are plotted in the graphs as "Average of Three Diets."

In 1917 this protein consumption factor was isolated as one of the reasons for the high variability of blood urea concentrations in normal human individuals (32), but recently we have defined its effect more precisely. Ten healthy men took 0 5, 1.5 and 2 5 gm of protein per kilogram of body weight during successive periods, and their plasma urea concentrations were determined twice on the fourth and fifth days of these three levels of protein consumption. The concentrations found *in five normal students on the sixth* day of a very low protein diet (5 gm per day) is also given (Table 13).

TABLE 13

EFFECT OF CHANGE IN PROTEIN CONSUMPTION ON THE BLOOD UREA CONCENTRATION OF NORMAL MEN

PROTEIN CONSUMPTION	AVERAGE	MINIMUM	MAXIMUM
gm per k	mgm per 100 cc	mgm per 100 cc	mgm per 100 cc
0 06	12.7	10 1	16 2
0 5	23 2	19 9	28 1
1 5	35.7	26 5	46.3
2.5	43 0	34 7	53.0

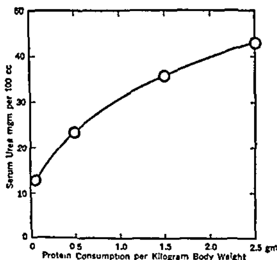


Fig. 13. Blood urea concentration of normal men on varying protein intakes.

The average *concentrations rise from 13 mgm per 100 cc on 0 06* gm, to 23 mgm% on 0 5 gm, to 36 mgm% on 1.5 gm, to 43 mgm% on 2.5 gm protein per kilogram. There is still a variability arising from other factors, but these observations leave no doubt that a knowledge of the protein consumption of our patients is necessary if we are to interpret the significance of moderate elevations of blood urea concentration.

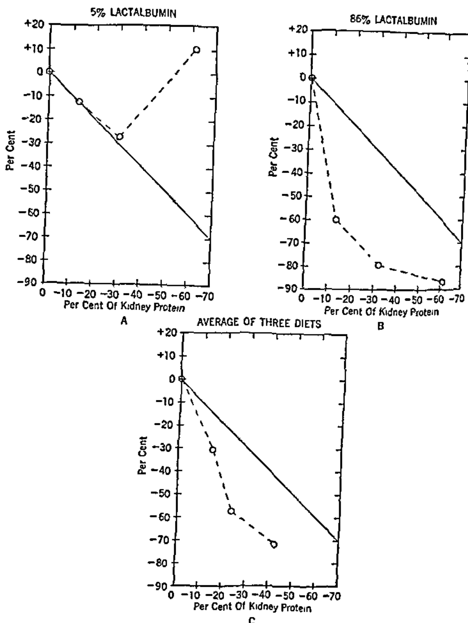


Fig 14. Concentration ratio.

pression that combines both of these measurements. This ratio gives the number of times by which the concentration of urea in the urine exceeds the concentration in the blood. This number has a concrete significance. It is one of the main factors that determine the osmotic work done by the kidney in separating urine with a high urea concen-

tration from blood-plasma in which the urea concentration is always much lower.

The relation of this quantity to the amount of renal tissue is given in Figure 14.

It can be seen at a glance that there is no direct or constant relation between the urea concentration ratio and the amount of renal tissue. When the concentrations are low, as in the 5% lactalbumin experiment, there is not even consistency with respect to the direction of change, and with higher concentrations the ratio values decrease out of proportion to the decrease in renal tissue.

UREA CLEARANCE

Directly, by weighing the kidneys in healthy rabbits (34), dogs (35), and rats (36), and indirectly, by the constancy of the values obtained in normal men after correction for body size (37), we know that the urea clearance can give us an approximate measure of the amount of functioning renal tissue. This is true, however, only when certain rather extreme conditions are fulfilled. These are not complied with in the experiments we are discussing. Here, as in the case of the other measurements we have dealt with, we are not testing the precision of any method, we are only observing how these measures change with change in kidney size under conditions almost wholly uncontrolled. Furthermore, even though some control of conditions adequate to meet the general requirements of clinical work were to be contrived, we know that there are still technical reasons why the urea clearance cannot as yet become a clinical method. Nevertheless, there is something of interest in these clearances in relation to the general question as to how we are to predict the extent of a renal lesion.

In Figure 15 it is shown how the ratios between the 24-hr urine urea excretion and the serum urea concentrations behave when the kidney is reduced in size.[8] Except with the most extreme reduction on a low protein diet, there is a fairly direct correspondence.

What is really instructive is the manner in which the absolute values of the urea clearance change when the protein concentration of the diet is altered, independently of any decrease in the amount of functioning renal tissue. This is shown in Table 11 in which the clearances of the control rats with whole kidneys, with the corresponding rates of excre-

[8] See footnote on p. 104 relative to 24 hr creatinine clearance derived from dividing a 24 hr rate by a single serum creatinine concentration. The same considerations apply to 24 hr urea clearances, though with urea the errors involved are greater than for creatinine and are of such a nature that they exaggerate the degree of increase in clearance with rising protein consumption (discussed later). However, for purposes of general orientation, these 24 hr clearances have their use, as long as we are fully aware of their unreliability as quantitative measurements.

obtained by noting its effect on the rate of urea excretion. The relation between the clearance values and the rate of urea excretion is shown in Figure 16.

The relation shown in Figure 16 is remarkable when we consider that everyone who has investigated the connection between the rate of urea excretion and the clearance has found that under constant physiological conditions the clearance remains constant no matter how much the rate of excretion or the serum urea concentration is varied. Here we find the opposite. And this is not something peculiar to the rat. This happens also in man when the observations are made under similar conditions, these "conditions" amounting to no more than the subject being left to his own devices except that he lives on foods that provide increasing amounts of protein. The results given in Table 15 were obtained from sixty measurements on ten interns and residents engaged in their usual clinical duties who, during three successive weeks, consumed 0.5, 1.5, and 2.5 gm of food protein per kilogram body weight, the results are plotted in Figure 17.

TABLE 15

Urea Clearance in Men with Increasing Protein Consumption

	Protein consumption (in gm per k)		
	0 5 gm per k	1.5 gm per k	2.5 gm per k
Clearance (l per 24 hr)	48 1	73 1	93 1
Rate of excretion (mgm per 24 hr)	11,193 mgm	25,909 mgm	39,763 mgm
Plasma concentration (mgm per 100 cc)	23 2 mgm %	35.7 mgm %	43.0 mgm%

Here also, in man, the species in whom the constancy of the clearance through all variations in rate and concentration is best documented, we find that every increase in rate and concentration induced by an increasing protein consumption is associated with an increase in the magnitude of the clearance.[9] The volume of plasma cleared of urea in 24-hr in-

[9] In spite of the ill-defined conditions under which they were measured, the data given in Table 15 follow quite closely the order expressed in the following equation:

$$\text{Clearance} = K \times \frac{\text{rate of urea execretion}}{(\text{serum urea\%})^2}.$$

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creases from 48 to 73 to 93 liters as the quantity of protein consumed increases. But this 93 liters is not the maximum. We found that, for a time, the clearance became constant at 120 liters per 24-hr when diuresis was induced by urea and water (37). Even this figure may be exceeded, for we observed clearances in man that approximated 170 liters of blood cleared in 24-hr when glutamic acid was ingested and a pronounced diuresis was established by the drinking of water (39).

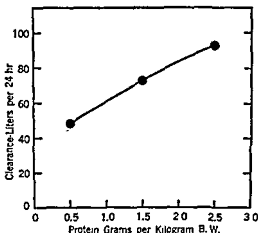


Fig. 17 Food protein and urea clearance The increase in the 24-hr urea clearance in normal men given diets that provided 0.5, 1.5, and 2.5 gm of protein per kilogram body weight.

This relation between the clearance and the level of protein consumption is too progressive and orderly to be written off as a mere consequence of the action of uncontrolled variables; there is clearly a factor at work here that breaks through all the chance fluctuations of daily life. It is much more important for clinicians than for physiologists that this protein consumption factor should be appreciated and comprehended. They can eliminate it. We cannot. Our patients come to us with wide divergences in the quantities of protein they customarily take, and the mode of excretion of urea—the most important constituent in the urine—will fluctuate widely in accordance with these habits

Nevertheless, it is the physiologists we have to thank for such understanding as we command. It is they who have shown that the rate of glomerular filtration is constant as long as the rate of blood flow (and presumably the relative tonus of the afferent and efferent glomerular arterioles determining the pressure within the capillaries of the tuft) remains constant. The constancy of the urea ratio when large quantities of water and urea are given to men who have not eaten for 15 to 17 hr

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TABLE 15

URFA CLEARANCE IN MEN WITH INCREASING PROTEIN CONSUMPTION

	PROTEIN CONSUMPTION (IN GM PER K)		
	0.5 gm per k	1.5 gm per k	2.5 gm per k
Clearance (l per 24 hr)	48 l	73 l	93 l
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$$\text{Clearance} = K \times \frac{\text{rate of urea execretion}}{(\text{serum urea\%})^2}.$$

Nowadays there is no danger that anyone will be taken in by a formula of this sort unless it is some really "pure" scientist, that is, someone who has grown innocent of the complexities of real life through long absorption in the study of his material under highly isolated and artificial conditions The experience of ordinary people, and particularly of ordinary doctors, renders them immune to such pretentious simplicities—pretentious because they give the impression that they describe a constant physiological mechanism, and simple, in the worse sense of that word, because they present a sequence of results derived from a hodgepodge of conflicting factors in the form and under the guise of a general law—a procedure that in general is simply wrong Nevertheless, this equation, however empirical and devoid of physiological significance it may be, does describe the average relation between the rate of urea excretion and the serum urea excretion under the complex of conditions that usually exist in "ordinary life." This was a clinician's first approximation. It is Ambard's "first law of urea excretion" (38).

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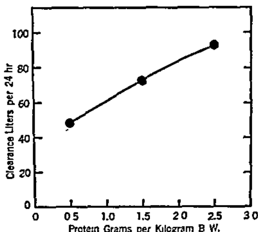


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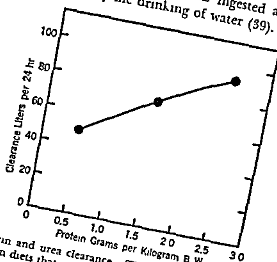


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weights—two rates for each level of protein consumption and for each subject.

If it is true that the quantity of creatinine daily produced and excreted in the urine depends on the mass of muscle tissue, it should be possible to correct these rates by some function of the body weights of the individuals from which they were derived, since, in general and apart *from obvious instances of obesity, the heavier* a man the more muscle he is likely to possess. Now the average relation between change in body weight and muscle weight is not known, but we can make various assumptions, correct the data accordingly, and judge that one to be best which gives us the smallest coefficient of variability. The simplest and most used correction is to suppose that as body weight increases there is a directly equivalent increase in muscle weight. With this correction the coefficient of variability of all the rates is $\pm$ 14.08%. If we take height as well as weight into consideration and use the DuBois formula for the calculation of body surface, the variability is reduced to $\pm$ 12.7%. There may be some justification for relating heat production and body surface, but there is no obvious reason why the amount of muscular tissue should vary with the extent of the body's surface area, and it may well be that *this reduction in variability has nothing to do with* surface but arises because surface formulas approximate the 0.7th power of the body weight. If that were so, the relation between muscle weight and body weight would be of the same type as we know exists for many other parts of the body and would follow the general formula, $y = ax^b$. When we give b, which is a power of the body weight, the successive values 0.6, 0.7, 0.75, and 0.8, the respective coefficients of variation of the creatinine rates are found to be $\pm$ 12.3%, $\pm$ 12.2%, $\pm$ 13.1%, and $\pm$ 13.4%. Therefore, in trying to eliminate the effect of the variation in the body *weight of our subjects, we shall get the most uniform results* if we multiply the observed rates given in Table 16 by the factor $\frac{70^{0.7}}{B.W.^{0.7}}$ and thus obtain the rates of creatinine excretion to be expected if all the subjects had weighed 70 kilograms.[10] These corrected rates are given in Table 17.

In this table we have tried to eliminate errors in urine *collections*. There were five collections out of the sixty in which unusually low

[10] In his book *Bioenergetics and Growth* (Reinhold Publishing Corporation, 1945), Brody shows that in mature animals of various species the rate of excretion of creatinine nitrogen varies as the 0.896th power of the body weight (C. N. = 12.7 B.W.$^{0.896}$). This is true for "endogenous" creatinine excretion, i.e., for measurements made on a creatinine free diet low in protein but adequate in calories. This relation contrasts with the behavior of total nitrogen excretion which, under the same conditions, varies as the 0.72nd power of the body weight (N = 14.6 B.W.$^{0.72}$). We mention this to show that no general significance can be attached to the fact that in our few observations made under other conditions ...ion varies as the 0.7th power of the body weight.

TABLE 17

CORRECTED RATES OF CREATININE EXCRETION ON THREE LEVELS OF PROTEIN CONSUMPTION[11]

subject	body weight k	RATES OF CREATININE EXCRETION (IN MGM PER 24 HR) 0.5 gm protein per k 4th day	0.5 gm protein per k 5th day	1.5 gm protein per k 4th day	1.5 gm protein per k 5th day	2.5 gm protein per k 4th day	2.5 gm protein per k 5th day
L	97.9	1,591	1,790	1,721	1,669	2,008	1,569
P	95.1	1,816	1,750	1,880	2,026	1,929	1,749
D	88.9	1,366	1,402	(1,546)	1,546	1,708	1,706
S	82.5	1,494	1,475	(1,598)	(1,598)	1,819	1,593
H	80.3	1,577	1,566	1,934	1,611	2,028	1,941
Po	77.0	1,771	1,616	1,935	1,803	(1,936)	1,936
R	76.0	1,469	1,489	1,745	1,701	1,910	1,868
Sh	73.4	1,879	1,797	1,985	1,872	2,039	2,216
K	65.5	1,876	1,900	1,858	1,967	2,197	2,072
W	57.5	1,608	1,527	1,554	1,778	1,921	(1,921)
Averages		1,638		1,766		1,903	

[11] Corrected to a body weight of 70 k by the factor $\frac{70^{0.7}}{B.W^{0.7}}$. The figures in parentheses are not derived from the actual observations because, in these cases, there was evidence of incomplete collection and they were replaced by the results obtained under similar conditions when no such errors were made.

creatinine rates were associated with unusually low rates of urea, sodium chloride, and water excretion. These suspected errors were replaced by the duplicate measurements made on the same level of protein consumption. Even so, we do not reach any high degree of constancy. Thus, if we eliminate the effect of increasing food creatinine consumption and consider only the rates obtained when 0.5 gm of protein per kilogram was taken, we find the corrected values vary from a minimum of 1,366 to a maximum of 1,900 mgm per 24 hr. This does not mean that the well-supported hypothesis of a direct relation between muscle mass and creatinine excretion is denied, for the variation may be a result of the obvious fact that no function of body weight can be expected to predict with any precision the amount of muscle tissue. The minimum in this instance was obtained from a tall, asthenic individual and the maximum from a short, muscular subject. Nor does it mean that we can afford to do without any correction. We cannot reasonably compare the creatinine excretion of a 100-kilogram with that of a 50-kilogram man. We have to use the best correction we can get, and we can be sure that, though far from perfect, it is much better than none at all.

In Table 17, the corrected averages rise from 1,638 to 1,766 to 1,903 mgm of creatinine per 24 hr as the protein consumption increases from 0.5 to 1.5 to 2.5 gm per kilogram. But this does not mean that protein, as such, has any effect on creatinine excretion, for the increase may be explained as a consequence of the fact that increasing quantities of preformed creatinine were taken as more and more cooked meat was con-

of creatinine and urea. The creatinine concentrations are given in Table 18, and in Figure 19 the percentage deviations from the general average of all observations are contrasted.

TABLE 18

SERUM CREATININE CONCENTRATIONS TAKEN BEFORE LUNCH ON THREE LEVELS OF PROTEIN CONSUMPTION

	SERUM CREATININE CONCENTRATIONS (IN MGM PER 100 CC)					
	0.5 gm protein per k		1.5 gm protein per k		2.5 gm protein per k	
subject	4th day	5th day	4th day	5th day	4th day	5th day
L	1.24	1.36	1.30	1.32	1.21	1.21
P	1.20	1.30	1.37	1.32	1.24	1.24
D	1.05	1.58	1.16	1.12	1.10	0.99
S	1.05	1.07	1.20	1.15	1.13	1.05
H	1.04	1.10	1.05	1.15	0.99	1.07
Po	1.20	1.20	1.20	1.20	1.12	1.07
R	1.02	1.05	1.08	1.06	1.05	0.97
Sh	1.12	1.12	1.15	1.15	1.05	1.13
K	1.12	1.23	1.16	1.28	1.12	1.19
W	1.05	0.99	1.15	1.05	1.05	0.99
Averages	1.15		1.18		1.10	

The average *serum creatinine concentrations are more constant* than the average creatinine rates of excretion. This is due in the main to two factors. First, we are dealing with a concentration, so that variation in body weight makes no difference, and we are thus delivered from the errors necessarily involved in any body weight correction system; and second, the effect of variation in the amount of preformed creatinine in the food was avoided because we took the blood samples after breakfast but before lunch. *Breakfast is a substantially creatinine-free meal* in the United States. Even if bacon is taken it is heated for such a short time that it is unlikely that any appreciable amount of creatinine is formed. The creatinine taken at dinner on the day preceding the collection of blood would have been already excreted, and the conditions thus approached those that would have been reached if the diet had been entirely creatinine free. This constancy of serum creatinine concentration *in normal individuals supports the idea that the source of creatinine is* the relatively constant store of creatine in the muscle fibers.

We have dealt with creatinine measurements made in normal individuals, under the variable but usual conditions of ordinary life, and have found them much less inconstant than the same urea measurements It remains to be found whether, under ordinary conditions, there is any relatively constant relation between any creatinine function and the total amount of effectively functioning renal tissue.

Creatinine Measurements and the Amount of Effectively Functioning Renal Tissue

For the purpose of general clinical orientation, we had resource to the same method we used for urea, that is, we observed the effect of the removal of varying proportions of the total renal mass. Before discussing these results it is proper to consider the reliability of the determinations of serum creatinine concentration in these experiments and in those we have just described. From the chemical point of view all of these figures lack the precision we can claim for our blood urea concentrations. This is due not only to the technical difficulties, in themselves not inconsiderable, involved in the estimation of minute creatinine concentrations, but arises mainly because the color that is measured may be due not to creatinine but to some unknown chromogen that gives the Jaffé reaction with alkaline picrate, a fact first revealed by Miller and DuBos (43). At low levels of creatinine concentrations in man, they found that creatinine accounted for almost all of the color, but we have no assurance that this is true for rat serum. The figures we give were obtained by measuring the color developed in the manner recommended by Folin and Wu in a photoelectric colorimeter (Evelyn). We were thus able to get a greater precision of color measurement than was possible for low concentrations with ordinary colorimeters, but we subsequently found that a still greater accuracy could be obtained by adding temperature constancy, exact timing, and known picric acid concentrations instead of the saturated picric acid solutions we used at first. But none of these refinements overcome the fundamental doubt as to what we are measuring—a doubt that would certainly stop a chemist but that leaves us free to carry on since our end is wholly empirical and clinical. As far as we know, these reservations refer only to the serum creatinine concentation measurements. There is no reason to suppose that the creatinine rates were not highly accurate.

The results we now report were made on the same animals on which the urea measurements were made, and our urea and creatinine results are thus strictly comparable.

Creatinine rates of excretion, like urea rates, do not decrease when the amount of renal tissue is reduced, but, unlike urea rates, they are not to any appreciable degree influenced by the amount of protein that is consumed. Both of these points are demonstrated in Table 19 where we give creatinine rates with varying degrees of reduction in the amount of renal tissue 1 week after operation on two levels of lactalbumin consumption, 5% and 86%. The rates given have been corrected for body weight differences on the assumption that both quantities vary as the

CREATININE MEASUREMENTS IN MAN

In man we cannot cut off part of the kidney, nor can we derive any direct measure of its anatomical size that is independent of function. Nevertheless, we can make an indirect, statistical prediction of the kidney weight based on the supposition that in man, as in other mammalian species, the kidney weight will vary as some power of the body weight. Here also we may anticipate that variation in protein consumption will be a major cause of error in predictions based on body weight. But if we take a group of healthy young men—those who acted as subjects for the observations in which the behavior of urea and creatinine rates and concentrations were contrasted (page 95)—we may expect to find that the quantity of effectively functioning renal tissue per unit of body weight will approximate a constant and will provide that anatomical yardstick without which our functional measurements cannot be compared or related to anything beyond themselves. For our purpose we will judge that functional measurement to be the best, which, in addition to other attributes, will itself possess the relative constancy we assume for renal mass where protein consumption is relatively constant.

At this point we can use our experiments on rats in order that we may not waste time in the investigation of certain measurements that cannot fulfill our clinical requirements. We have shown that the size of the kidney may be markedly reduced without any reduction in excretion (Table 19), and so the rate of creatinine excretion is eliminated. The concentration of creatinine in the urine may also be neglected because it never approaches that maximum concentration at which we might anticipate a direct relation to kidney size (page 82). The measurement that all experience suggests is the one most likely to give us what we want is the creatinine clearance, and so we shall first consider the clearances in the residents and interns. We are assuming that they all had kidney weights that would be about the same when expressed as grams per 0.7th power of their body weight in kilograms so that, if creatinine clearances varied as the weight of their kidneys, we should expect them to show a like degree of uniformity.

The clearances obtained by dividing the corrected 24-hr rates of creatinine excretion by the serum creatinine concentrations measured before lunch on the three levels of protein consumption are given in Table 20.[12]

[12] This procedure involves the assumption that a meaning can be attached to clearance values obtained by dividing creatinine rates measured over a 24 hr period by a single serum creatinine concentration measured at 9 A.M It is not likely that anyone with practical experience in the measurement of clearances will be willing to suppose that clearances obtained in this way are likely to have any very precise quantitative significance. "Sig-

TABLE 20

24-HR CREATININE CLEARANCES* ON THREE LEVELS OF PROTEIN CONSUMPTION

	CREATININE CLEARANCES (IN L PER 24 HR)					
	0 5 gm protein per k		1.5 gm protein per k		2 5 gm protein per k	
subject	4th day	5th day	4th day	5th day	4th day	5th day
L	128	132	132	127	166	130
P	151	135	137	153	155	141
D	130	89	108	138	155	173
S	142	138	115	126	161	152
H	152	142	184	140	205	182
Po	148	135	161	150	157	181
R	144	142	162	161	182	193
Sh	168	161	173	163	194	196
K	168	155	160	154	196	174
W	153	155	135	169	183	149
Averages	143		147		171	

* Corrected 24-hr creatinine rates of excretion divided by the serum creatinine concentration observed at 9 A M.

The average clearances for the three levels of protein consumption given in Table 20 are 143, 147, and 171 liters per 24 hr, and so it is clear that there was some factor associated with the 2.5-gm protein consumption per kilogram that increased the clearance value. One very probable reason for the considerable increase of clearance value on the 2.5-gm level was that this level of intake was reached by the consumption of considerable quantities of cooked meat at lunch and dinner. The creatinine in this meat augmented the 24-hr creatinine excretion rates (Table 17) but did not increase the creatinine concentration of the blood serum taken before lunch (Table 18). But there is more than this factor involved, for in other experiments (reported elsewhere) we find clear evidence of a rise in creatinine clearance values with increasing protein consumption that cannot be thus explained With better reason than can be assigned to our interpretation of the increase in urea clearances when the kidney size remains constant and only protein intake is changed (page 92), we believe that part of this observed increase in creatinine clearance must be assigned to increase in rate of blood flow and pressure changes in the glomeruli.

In clinical work it is not hard to exclude such unusual diets as are represented by this 2.5 gm per kilogram of body weight protein consumption. It is done in every office and clinic in which the dietary habits of new patients are surveyed. So it is quite practical and reasonable for us

nificance," however, is a relative term dependent on the sort of question the measurement is designed to answer We are at present investigating the extent of the error involved [illegible]

[illegible] night.

posite of the lemon color of sodium picrate and a minute amount of deep-orange-colored creatinine picrate, and we have to keep the sodium picrate constant *if we are to measure the creatinine.*

In most patients the colors will be the same before the diluting fluid has brought the volume to the 15-cc mark in the urine tube. Whatever the reading may be, the clearance is obtained by dividing that reading in cubic centimeters by 1.5. If the reading is 15 the clearance is 10; if *14 cc it is 9.3, and so on. Occasionally* the 15-cc mark may be reached and the color is still deeper than in the serum tube. In such a case 1.5 cc of the thoroughly mixed fluid is transferred to another tube and the dilution cautiously continued until the colors match. If this 1.5-cc quantity, which is $\frac{1}{10}$ of the total, has to be diluted to 3 cc, then the *number of times by which the urine* exceeds the serum creatinine is $10 \times \frac{3\text{ cc}}{1.5\text{ cc}}$, or 20 times. In uremic patients the urine color after 10 min may be weaker than the color in the serum tube. In that case the diluted alkaline picrate is added to the serum tube. If the original 1.5-cc volume had to be diluted to 3 cc, the ratio is obtained by multiplying unity by $\frac{3}{1.5}$, and the result would be 0.5. These ratios of 20, 10, or 0.5 can be conceived in a less abstract manner if they are regarded as volumes of 20 cc, 10 cc, and 0.5 cc of plasma "cleared" of creatinine by the kidney in 1/1,000 of 1 hr, which is 3.6 sec. The units of measurement we used were chosen because they were convenient in mechanical manipulation and are better translated either into the units used by physiologists, which are cubic centimeters of plasma cleared in 1 min, or into clinical terms which are liters of plasma cleared in 24 hr. These are all directly proportional to one another and can be obtained by *multiplying the clinical* measurement by 5.5 to get the physiological and by 8,000 to get the clinical expression (Table 21).

TABLE 21

CONVERSION OF CLINICAL MEASUREMENTS OF CREATININE CLEARANCE INTO PHYSIOLOGICAL AND CLINICAL UNITS OF MEASUREMENT

CLINICAL MEASUREMENT	PHYSIOLOGICAL UNITS	CLINICAL UNITS
0.3 cc plasma in 3.6 sec	plasma in 1 min, cc	plasma in 24 hr, liters
0.5	2.8	4
10.0	55.5	80
20.0	110.0	160

Before this translation the clinical measurement should be corrected *by multiplying by a factor* opposite the patient's body weight in a table given in Table 22. This is a correction based on the supposition that

the rate of creatinine excretion, and therefore the clearance, varies as the 0.7th power of the body weight, and it has the effect of giving the clearance in terms of the one that would have been given if the patient had weighed 70 kilograms. In actual clinical work we have found it convenient to by-pass all specific units and to express the results in terms of the percentage of the average normal creatinine clearance of 146 1 per 24 hr taken as 100%, and this mode of expression is simply obtained by reading it from a table.

TABLE 22

FACTORS FOR CONVERSION OF CREATININE CLEARANCES FROM PATIENTS OF VARYING BODY WEIGHT TO THE CLEARANCE TO BE EXPECTED FOR A SUBJECT OF 70 KILOGRAMS BODY WEIGHT

BODY WEIGHT	FACTOR	BODY WEIGHT	FACTOR	BODY WEIGHT	FACTOR
kilograms		kilograms		kilograms	
10	3 91	47	1 33	84	0 88
11	3 76	48	1 31	85	0 88
12	3 61	49	1 29	86	0 87
13	3 46	50	1 27	87	0 86
14	3 30	51	1 26	88	0 85
15	3 15	52	1 24	89	0 85
16	3 00	53	1 23	90	0 84
17	2 85	54	1 21	91	0 83
18	2 70	55	1 20	92	0 83
19	2 56	56	1 19	93	0 82
20	2 40	57	1.16	94	0 82
21	2 35	58	1.15	95	0 81
22	2 29	59	1 13	96	0 80
23	2 23	60	1 11	97	0 80
24	2 17	61	1 10	98	0 79
25	2 11	62	1 09	99	0 79
26	2 05	63	1 08	100	0 78
27	1 99	64	1 07	101	0 77
28	1.93	65	1 06	102	0 77
29	1 87	66	1 05	103	0 77
30	1 81	67	1 04	104	0 76
31	1 78	68	1 02	105	0 76
32	1 74	69	1 01	106	0 75
33	1 71	70	1 00	107	0 75
34	1 68	71	0 99	108	0 74
35	1 65	72	0 98	109	0 74
36	1 61	73	0 97	110	0 73
37	1 58	74	0 97	111	0 72
38	1 55	75	0 96	112	0 72
39	1.51	76	0 95	113	0 72
40	1 48	77	0 94	114	0 71
41	1.46	78	0 93	115	0 71
42	1 44	79	0 92	116	0 70
43	1 42	80	0 91	117	0.70
44	1 40	81	0.91	118	0 70
45	1 38	82	0 90	119	0 70
46	1 35	83	0 89	120	0 69

This is a quick and simple method applicable under almost all out-patient conditions. But perhaps in sparing time and effort we have lost so much in precision that the results no longer have any clinical value? In some degree this very proper doubt will be met by an inspection of Figure 22. Here we have plotted the first clinical results we

experience, are better equipped than they to understand the wisdom of George Meredith's couplet:

> Ah, what a dusty answer gets the soul
> When hot for certainties in this our life! *

Certainty is what forever eludes us, and we are eager to get our hands on any truth, no matter how incomplete and mixed with error.

DIRECT CLINICAL METHOD FOR ESTIMATING SERUM CREATININE CONCENTRATION

We have described in detail how to measure creatinine clearances in this clinical manner because they are useful when no color standards and no apparatus beyond what everyone possesses are available. This is a quick and simple method. Yet, on days when more than the usual number of new patients appeared, we found that it was not quick enough for us, and so we began to cast around for some procedure even more expeditious. One day, in connection with some other problem, the question arose as to whether alkaline sodium picrate could be added to serum without precipitating the proteins. When some alkaline sodium picrate we had been using for creatinine clearances was added to serum, the mixture was found to remain quite clear, and as the tube was being watched it was observed that the orange color of creatinine picrate was beginning to appear. The tube was laid aside, and when it was picked up again an hour or so later it was seen that, though it was still quite clear, it had taken on a very deep orange color, far deeper than that which could have been derived from the creatinine content of the serum we were using. It was obvious that there was something else in the serum besides creatinine that was giving the Jaffé reaction. We might have given up the dawning hope of getting direct creatinine readings without removing the serum proteins if it had not occurred to us that creatinine and this unknown chromogen might have entirely different rates of reaction. To test this hypothesis, alkaline sodium picrate was added to serum, and the rate of development of light absorption at a wave length of 520 A, the peak of the absorption band of creatinine, was measured in a spectrophotometer. The results are shown in Figure 23.

It will be noted that when alkaline sodium picrate is added to whole serum, the rate of development of creatinine picrate is extremely rapid—even more rapid than in protein free filtrates—so that 6 min after the addition the curve is already asymptotic. However, the color development does not stop but slowly and steadily increases until, after several hours have passed, it is far deeper than that given by any creatinine

* *Poetical Works of George Meredith*, "Modern Love," p. 155. New York Charles Scribner's Sons, 1928.

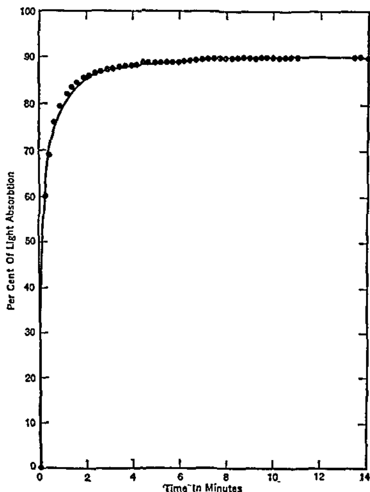


Fig. 23. Rate of color production at wave length 520 after adding 10 cc of diluted sodium picrate to 5 cc of serum.

concentration that ever occurs in man. With such a wide difference in the rates of reaction of the creatinine and the chromogen, it seemed as though we ought to be able to measure the creatinine alone if we read the color exactly 6 min after the addition of the picrate to the serum. This was shown to be possible when spectrophotometric readings were made in sera to which known amounts of creatinine had been added.

It has probably occurred to our readers that if it is true that the rate of creatinine excretion remains the same, no matter how much we reduce the size of the kidney, it must follow that the correspondence between the value of the creatinine clearance and kidney size is entirely due to

TABLE 24

MAXIMUM ERRORS BY THE DIRECT CLINICAL METHOD

	CREATININE %, PHOTOELECTRIC METHOD	NO. OF PATIENTS	MINUS ERRORS	PLUS ERROR
Normal	0 9 — 2 mgm %	63	0 64 mgm % *instead of* 1.15 mgm %	2 10 mgm % ins 1 08 mgm %
Slight to Moderate Retention	2.1 — 5 mgm %	15	2 96 mgm % instead of 3 28 mgm %	2.96 mgm % inst 2.28 mgm %
Marked Retention	5.1 — 8 mgm %	9	7 10 mgm % instead of 7.90 mgm %	8.62 mgm % inst 7.62 mgm %
Uremic Levels	8 1—10 mgm %	6	7.90 mgm % instead of 9.34 mgm %	9 28 mgm % inst 8 13 mgm %

blood urea concentrations in most of the patients in whom the d method indicated any abnormality and in many of those whose creati readings were within the normal range, though it is true that this parison gives us only a rather rough and uncertain measure of reliab since the blood urea concentrations vary with extrarenal factors tha *not affect creatinine.*

In closing this discussion it would be easy to end in a neat and clusive manner. Of all methods we have asked the same question: ' they or do they not give results that vary as does the amount of renal sue left in rats from which varying proportions of their total kidney n have been removed?" On these experimental grounds, and also a consequence of observations made on normal individuals and on patie we have finally reached the conclusion that the best method is the de mination of the concentration of creatinine in the serum, and we h converted this determination into a clinical method by devising a ra and reliable procedure for its measurement. We might go further a say more. We have shown that the corrected rate of creatinine excreti remains constant no matter what the size of the kidney, and also t creatinine clearances seem to vary rather closely with our best estima of the quantity of effectively functioning renal tissue. From these o servations we can deduce a simple equation that will tell us, from t serum creatinine concentration alone, the extent of any renal lesion terms of a percentage of the normal amount of *renal tissue.*

If we abstain from expressing our conclusions in this manner it not because we would not like to think of the problem in exactly th way, but rather because we know that our data are inadequate to bea the weight of an expression that is at once so compact and so final. T speak in such terms would be equivalent to supposing that we ha reached the end of a journey of exploration on which, in fact, we hav scarcely started. We have looked over this country from a distanc

and have made a rough sketch of its main features, but when it is really penetrated we will probably find surprising and apparently conflicting features that will render any generalized abstraction not only inapplicable but misleading. Yet there is no harm in drawing these crude and faulty maps so long as we know what we are doing, and it is true that almost any map is better than none at all, since it at least gives us something definite to correct and extend. In clinical practice, which is within the field of the individual and concrete, this criticism and extension will be accomplished if we ourselves make those simple observations that give us a direct and specific knowledge of facts that bear on this problem of the extent of the renal lesion and will then go on to relate these facts to all the others derived from the patient's history, his physical examination, and the peculiarities we see in his blood and urine. Placed in this rich pattern of co-ordinated observations, there is little danger that the results of any single method will lead us far astray.

purposes. There should be at least a clinical, an anatomical, a physiological, and a biological classification, and, growing out of the endeavor to understand disease in a manner that satisfies these interests in all their internal and external relations, there may finally evolve a classification that might be called philosophical.

When, however, we try to describe clinical classifications under this category of purpose we do not find them all informed by any single endeavor. A clinician is complex. He is part craftsman, part practical scientist, and part historian; so his several classifications involve, in varying degree, all these elements. It is only if we look at him when he is working with his patients that we find him single-minded. Then he is wholly pragmatic and utilitarian. His only design is to bring relief, and he is not at all scrupulous about how he does it.

At that moment his classification is one in which diseases are distinguished in accordance with their "causes," meaning by causes not all the factors responsible for a situation but only those he can control—those whose elimination leads to the disappearance or diminution of disease. It is not an etiological classification, except insofar as it may give rise to the recognition and removal of some condition necessary for the development of disease. Once disease is established, the clinician pays no attention to etiology. Then he tries only to stop the disease by removing some factor required for its continuation. And when disease has run its full course, a clinician, insofar as he is merely a craftsman, reviews the process in order to make sure that all the "causes" were recognized and the appropriate actions taken. This is the primitive clinical classification. It is wholly subordinate to therapeutic action.

Physiologists and anatomists are not ruled by a desire to do away with or ameliorate disease. They seek rather to understand it, in the sense of being able to give a reasonable account of the mechanisms through which it operates. They avoid the word "cause," as used by clinicians, because for their purpose it is too anthropocentric. For them there is no one cause for any disease: there is a constellation of causes that are to be distinguished in accordance with the degree to which they are more or less directly concerned in bringing about alterations in the function and structure of the body. Disease is for them a quantitative change in the processes that initiate and continue function, or that develop or maintain structure. They view disease as a variant of normal form and function. Their purpose is to give an explanation of such aberrations in terms of mechanics. Their classification is ordered by their interests; it resembles an engineer's catalogue of the various defects that may arise in the operations and buildings of a factory.

Many of our present classifications are called pathological, but they

do not deserve that name. Pathology is not yet an autonomous science, and so these so-called "pathological" classifications are based on a medley of clinical, anatomical, and physiological principles and have no inherent unity. A truly pathological ordering of disease can develop only after it has been demonstrated that the alterations in mechanism occurring in disease are different in kind as well as in degree from those dealt with by anatomists and physiologists. Only when we know that the processes of disease obey laws distinct from those of anatomy and physiology will there be any need for a pathological classification.

There is another classification, broader and deeper than the anatomical or physiological but not yet quite explicitly formulated. Clifford Albutt dreamed of it in 1867 (45) and later gave it this outline

> We have made a minute clinical study of human nosology; perhaps, indeed, no extensive discoveries remain to be added to this field of research. But the parts into which disease has been dissected are not the elements out [illegible]
>
> [illegible] through the microcosm of the embryo, in pursuing disease also through its variations in space and under changed climatic conditions; in registering the effects as these changes pass by hereditary transmission from the dynamic to the static form and in so tabulating pathological sequences in family, race, or country as to detect the latent affinities of diseases apparently unkindred.

This, when we have achieved it, may be spoken of as a biological classification of disease.

Of all possible classifications the most universal will be what may be called the philosophical, but of this we have as yet only adumbrations. We may be sure only that it will overcome and yet include the abstraction of the scientific and the particularity of the clinical points of view, and that within it there will be room for the potential as well as the actual relations of disease to the individual, to society at large, and to the world in general. All other classifications are elements in its formation The emergence of this all-inclusive system will be best forwarded if all the disciplines interested in disease develop the implications of their own presuppositions to their logical conclusions, each of them quite conscious as to why they diverge from all the others.

Purpose and Nature of any Clinical Classification of Renal Disease

To separate for classification the diseases of the kidney from disease in general is already to have broken the initial rules of any sound sys-

peculiarities or the physiologists' comprehension of function, they are not placated. They regard such borrowings as a *prostitution of their* sciences for merely utilitarian ends.

This ancient misunderstanding of medicine still persists and of late has shown signs of exacerbation. So, particularly today, it is proper to preface any discussion of clinical classification with some sort of declaration of the freedom that should rightfully be accorded the clinician to make any sort of arrangement of his own or of anyone else's observations that, in his opinion, will forward the attainment of his own specific end.

If there are properly several fundamentally different ways of classifying renal disease, it is also true that within the strictly clinical field there *is need for more than one classification. But the distinctions between* clinical classifications do not arise from any difference in the underlying purpose for which they are used. This purpose, through all its many variations, remains always the same. Clinical classifications differ in accordance with the nature and extent of the data available for arrangement. Sometimes the observations are sketchy and incomplete, covering what has been seen and felt and heard at only one point in time. Sometimes they are detailed and exhaustive, including information as to the complex of conditions under which the disease had its inception, comprising a complete description of the gradual development of the disease process over many years, and ending with an account from the pathologist of what he found after the disease had run its full course. These two extremes must clearly give rise to different ways of ordering the data.

From the first, there can come nothing more than a provisional arrangement of possibilities, from the second, since there is here an extensive assortment of co-ordinated facts in series, there may be derived something less hypothetical, something more concrete and specific. Between these two extremes lie many possible clinical classifications exemplifying all gradations in the passage from almost pure speculation to almost complete certainty. A clinician does not value one of these more than the others They are his tools and he uses them all in turn as they fit the information he has at his disposal. He employs them to place each individual patient in relation to others in groups that have certain characteristics in common. Fitting the patient thus into a pattern, he is able to use for him the knowledge gained in the past from other patients in the same group; so that he knows in a general way what to expect and in a general way what to do. In medicine, classification is generalized diagnosis, but it is a fluid, constantly changing process of specification whose real significance is not to be obtained from tabulations in textbooks, no matter how "authoritative."

Although clinical classifications can be arranged in order, from the

achieved is other and more complex than that with which we started. This is true even though that second individuality is never taken quite seriously, is under constant revision, at no time has the body and substance that belongs to every one of our patients, and remains forever something approached but never reached.

The hope has been expressed that some day we may attain to a classification of disease that will begin to deserve the appellation "philosophical." No clinical classification will claim more than representation in that parliament of all the interests involved in the study of disease, but what has been said about clinical classifications is enough to make plain that none are more eager or more concerned than are doctors to forward this universal understanding.

We can claim, perhaps, to be as well prepared for this event as others, because the two-way method we use in the development of our classification approaches the method that by necessity is used in philosophy. In particular, we do not start with any consciously fixed and absolute postulates. When the results of our ratiocinations do not help us in action, we are quite willing to reconsider the plan we used in arranging our original facts of observation, not ignoring or doubting anything we have seen but hoping we may bring to light the prejudice, the ignorance, or the unconscious assumption that has caused our thinking to deviate.

Clinical Arrangement of Proteinurias

If there are good reasons for objecting to a separation of patients with diseased kidneys from all other patients, no one will even try to defend a division based on the presence or absence of protein in the urine. This is not classification at all. It is simply a necessary recognition of the local and transitory fact that our clinic accepts patients with proteinuria and rejects all others. The sieve through which they have to pass is even narrower because this is an out-patient department, and we only see the patients with proteinuria who are well enough to walk. Thus, by the very nature of our own requirements we are debarred from ever attaining to that breadth of vision which is one of the first prerequisites for classification.

Though what we see is thus only a small part of the whole, it is rich in diversity and covers more than we can comprehend or order intelligently, so that it is "as if one should see an immeasurable landscape through a keyhole." It will be remembered, moreover, that it was through a preliminary concentration on this one symptom of proteinuria, and his subsequent observation that it was invariably associated with renal disease, that Richard Bright laid the foundation of all the clinical knowledge we possess. Proteinuria and changes in the urinary sediment

are, in fact, the invariable and frequently the only direct evidences of active renal disease.

The multiplicity of clinical classifications that arises because of a progressive increase in our knowledge of patients as we continue our observations is paralleled in the succession of the arrangements into which ambulatory patients with proteinuria can be placed, but here we shall refer to only two—the first and the last.

FIRST ARRANGEMENT

Our first arrangement owes most of its peculiarities to the special methods we have described; it is thus provincial as well as provisional and does not warrant any extended consideration. Every physician has his own first-visit classification dependent on his own methodology, even those who may adopt methods analagous to those we are now using will employ them in a manner peculiar to themselves. In any case, first-visit classifications cannot be adequately described because they contain so much that is intuitive. The objective data are only a part of the evidence used. Mixed with the evidence are vague impressions derived from the appearance and behavior of patients—from all sorts of little things that cannot well be put into words. The manner in which these objective and subjective indications begin to take some definite form is largely determined by the degree of the physician's mental organization of his past experience. But this process of formulation is almost wholly implicit. It goes on in what we call "the back of our heads" and we become aware of its operation after its work has been done and something in our mind has clicked, or, to use longer words, only after we have achieved a hypothesis with respect to the general, sometimes even the specific, place the patient occupies in a more or less consciously formulated system of classification.

At the first visit, then, we are looking for a "lead," and until we get it our mind is not truly engaged. This lead is usually a hypothesis, not a conclusion, but until it is settled one way or the other it orders and directs our subsequent investigation. It may be quickly negated, and then we fall into a passive state of receptivity until we again get a new lead.

Now there is something to be said for the idea that these periods of passivity should not be too prolonged. There is always the danger that the mind may fall asleep, and one of the best ways to keep it awake is to have it supplied with a succession of pertinent objective data that are quick and final answers to these ever-rising questions. This requires the organized and co-ordinated work of a group.

While the doctor is taking the history and making his general physical

that have been told from beginning to end—those for which all the available facts are in and every etiological, clinical, and pathological observation assembled.

This means that in describing the last arrangement we shall exclude all the patients we are now treating, no matter for how long, because their stories are not yet finished. It means, also, that we shall have to eliminate a great number, perhaps the majority, for whom no evidence relative to their origin and development could be obtained. We have also excluded all cases, no matter how complete and convincing, that we have not followed by our own methods, so that our data might be strictly homologous and based solely on first hand observation. The most interesting of all our patients, those whom we have never been able to understand at all, have been left out. By virtue of all these exclusions and by choosing one patient as a symbol of certain, frequently seen forms of proteinuria, the experience of over twenty years up to 1941 has been condensed to the consideration of 412 patients who alone can be regarded as more or less suitable for the purpose of a last arrangement.

We know very well that we are evading any real discussion of diagnosis when we refuse to say anything at all except about what we call the first and the last arrangement of patients with proteinuria. For the first arrangement is so tentative that nothing definite *can* be said about it, and the last is so well documented that nothing *need* be said about it. Furthermore, this last arrangement of all the multitudinous problems raised by proteinuria is dull because it is so certain.

But before they came to their end there was nothing dull about these questions. At one time they were probabilities, not certainties Once they were developing and growing, and so were full of life and even danger, because it was sometimes necessary to take a chance and to act as if they were not problematical but sure. When they were finally answered, these questions died. The last arrangement is their graveyard in which they lie symmetrically deposited under their more or less appropriate epitaphs.

THE LAST ARRANGEMENT

I. Caused by toxic material reaching the kidney through the blood stream. *Associated with evidence of a degenerative renal lesion.*
  - A. Mercury poisoning.
  - B. Industrial solvents.
  - C. Sulfa drugs.
  - D. *Haemoglobin and its derivatives.*
  - E. By-products of infectious diseases (febrile albuminuria).
  - F. Myxedema.

G. Gout.
H. Amyloid disease.
I. Pregnancy toxemia.

2. Caused by abnormalities in plasma protein formation? Associated with evidence of a degenerative renal lesion.
3. Caused by decrease in the blood supply to the kidney. Associated with evidence of a degenerative renal lesion.
4. Caused by neoplastic disease in the kidney. Associated with evidence of a degenerative renal lesion.
5. Caused by developmental anomalies of the renal artery, vein or urinary tract.
6. Caused by developmental anomalies of the kidney.
7. Caused by diseases of the renal arteries.
   A. Disseminated lupus.
   B. Periarteritis nodosa.
   C. Symmetrical necrosis of the cortex.
8. Caused by hypertension. Associated with evidence of a more or less gradual decrease in blood supply.
9. Caused by bacteria growing in the kidney.
   A. Tuberculosis.
   B. Chronic pyelonephritis.
10. Caused by bacteria in the blood that induce glomerulitis.
11. Caused by B hemolytic streptococci that initiate glomerular nephritis.

CHAPTER 6

THE DIFFERENTIATION OF GLOMERULAR NEPHRITIS FROM OTHER DISEASES

To provide some sort of system in the discussion of the diseases that have to be distinguished from glomerular nephritis, we shall use what we called the "last arrangement" of proteinurias given at the end of the preceding chapter. For the moment this is as good a sequence as we can contrive, though the arrangement is not logical, for there is overlapping between the divisions; it is not anatomical, for under one or another heading are conjoined instances of extremely diverse structural defects; it is not physiological, for we have paid no attention to the nature of the functional abnormalities that are included; it is not biological, for it is not ordered in accordance with principles derived from any understanding of how the diseases enumerated can be viewed as deviations from the laws followed by the processes of life; and certainly no one could say that it is in any way tinctured by considerations of a philosophical nature. This is a clinical arrangement made for the purpose of facilitating treatment. It is intended to separate patients into groups for each of which a specific therapeutic strategy is required. We are well aware that this is no more than an inadequate and faulty beginning of an attempt to classify patients with proteinuria in accordance with their therapeutic needs. It may, however, be taken as a symbol of our recognition that any classification purporting to be clinical should be based on this principle.

The number of patients in the eleven groups that we have been able to follow from beginning to end gives, of course, no index as to the distribution of renal disease among the population at large, and it has no meaning even for that section that visits out-patient departments. Our collection is heavily overweighted with examples of glomerular nephritis because our clinic was known to be particularly interested in that disease. Simply as a list of diseases associated with proteinuria it is quite incomplete. The reader will be able to add many more from his experience as, indeed, we could from our own. Those we mention are the principal ones we have recognized as distinct diseases that we are sure are not glomerular nephritis. But this knowledge is a small begin-

ning, not an end. The real interest and all the future belongs to the diseases we do not mention because we know so little about them that we cannot even give them a name. It is from the patients that have suffered from these unknown diseases that the classification of tomorrow will grow.

Because our subject is the treatment of glomerular nephritis, we shall mention only some of the more salient features of the diseases with which it may be confused, selecting, for the most part, those that have a direct bearing on such questions as arise in office practice or on the interpretation of the results of the special methods we use in our clinic. We say nothing at all, for instance, about that perennial problem of the ward—the question as to whether a patient in the last stages of uremia is coming to his end because he has a glomerular nephritis or because his kidneys, and all else besides, are failing as a final consequence of extreme hypertension. Not only is this not an out-patient question, it is a therapeutically useless question, and this is a book about treatment. But we must be allowed to say a word, now and then, about the treatment of diseases that are not glomerular nephritis in order to delimit the scope of the therapeutic principle with which we are concerned.

The first group, containing renal lesions caused by toxic material reaching the kidney through the blood stream, is a hodgepodge of diseases arising in widely different ways, pursuing wholly different courses, and coming to many different ends. The list we give is only a sample, for it is into this group that the majority of all patients with proteinuria fall. Nevertheless, from the point of view of the grand strategy of treatment, all these patients, with all their diverse diseases, make one group because in every one of them the proteinurias we see, and the often very interesting changes in the kidney that we detect, are not matters of real moment but only observations to be noted and quickly passed by on our way to deciding what it is that is damaging not only the kidney but the patient, and what we can do to get rid of it. With every patient in this group we must forget the kidney because it is only by going beyond the kidney that there is clinical hope.

In every disease within this group the renal lesion is secondary to something wrong elsewhere, something that comes either from outside of the body altogether or something that is a by-product of disease in some other part of the body than the kidney

In every instance, too, the renal lesion is reversible. Get rid of the extrarenal cause and the renal disease will melt away A patient may be deeply uremic as a result of mercury poisoning, but a month or two later a pathologist will be hard put to it to find any indication of the necrosis of the proximal tubules that had so nearly killed him. Or the glomeruli

may be heavy with amyloid, but a *year or two after the amputation of a* leg with sinuses leading to dead bone not a trace of amyloid need be left. These are the renal lesions we can sometimes cure: never by treating the kidney, always and only by removing the cause.

The second group, the degenerative renal lesions caused by abnormalities in plasma protein formation, consists of patients who come to us because they are edematous, but, though the urine contains protein and there are signs of a degenerative renal lesion, the development, course, and outcome of their diseases is quite different from glomerular nephritis. We know very little about these patients, but it already seems clear that they are not all alike. We put them together because it would seem that in all of them our hope of developing a rational treatment depends on our capacity to find how to induce an increase in their capacity to *produce normal plasma proteins at an adequate rate.* Here also, as in the first group, the renal lesion is secondary, but this is a very special case because here the kidney itself participates in producing its own disease. Presumably the primary cause is the formation of proteins that can pass the glomerular filter in more than the normal concentration or of proteins that cannot be digested by the tubule cells; but the renal disease, the degeneration in the proximal tubule cells, is a self-poisoning through reabsorption of this filtered protein.

[illegible]

secondary in this instance to changes in the distribution and rate of flow of the blood with which it is supplied. We do not often see these patients in the out-patient clinic but in the ward. During war this becomes a daily problem for regimental surgeons in front-line dressing stations. Here also treatment goes beyond the kidney. (See Addendum on p. 178.)

The fourth group, the proteinurias caused by an infiltration of the structure of the kidney by neoplastic cells, that now and then occurs in the leukemias, Hodgkin's disease, and myeloma is, from the point of view of treatment, a division that is extrarenal.

The fifth group comprises a medley of all sorts of congenital defects in the structure and relationships of the renal artery, renal vein, and urinary tract. Some of the patients in this group can be cured by surgeons; there are others, in whom no possibility of any rectification of *the anomaly exists, who should be treated by the dietetic* methods we recommend if the defect involves damage to the structure and function of the kidney itself. For us, however, the most common and therefore most important subdivision within this group is the *condition known as orthostatic* albuminuria.

With the sixth group we come to the first division in which the cause

is a congenital malformation that involves the kidney itself. There are several anomalies of this sort, but by far the most important for treatment and the only one we shall say anything about is polycystic disease.

In the seventh group, proteinurias caused by diseases of the renal arteries, we include the three curious and little understood conditions called disseminated lupus, periarteritis nodosa, and symmetrical necrosis of the cortex. The first two are systemic diseases, and it is only toward their close that the renal lesions sometimes become predominant and determining. In symmetrical necrosis of the cortex we have a condition in which the renal arterial lesion is central, and the outcome of which may at times depend on treatment directed specifically to the kidney, since here we have a lesion in which large blocks of nephrons die. (See Addendum on p 178.)

In the eighth group, the proteinurias caused by hypertension, we have patients in whom the renal manifestations are at first purely functional and who only later give evidence of anatomical renal defects which we ascribe to an increasing degree of arteriosclerosis and of thickening of the intima of the arterioles of the kidney. This is still a secondary lesion as far as the parenchyma of the kidney is concerned, and as for the arterial and arteriolar lesions there is no reason, in the vast majority of patients, to suppose that they are more than consequences of a systemic hypertension whose origin is extrarenal. So this is still a disease in which for treatment we must go beyond the kidney.

But what treatment? Here is a disease that everyone sees every day and no one understands, a condition at once so common that the man in the street knows a good deal about it and yet so obscure and complex that none of its students, either in the experimental or in the clinical fields of investigation, have been able to encompass it. Its treatment remains a problem from which all those who demand clear and definite evidence turn aside in distaste. Yet it is precisely here that the true clinician comes into his own. It is in this dubious warfare against an uncomprehended foe that he shows his true mettle, understanding—though he could not say how—the unexpressed anxieties and the hidden pressures that infringe upon his patient, taking him all in—not to analyze him but only in order to help him. The ways to help are as numerous as are the patients. For each of them there is one best way, though how to find it is not something we can read about in books or learn from psychologists. This is something the patient can tell us.

In the ninth group, diseases caused by bacteria growing in the kidney, there are a number of specific infections that might be mentioned. But for our purpose the all-important member is chronic pyelonephritis; important, again, from the point of view of treatment—direct treatment by minute amounts of sulfa drugs and indirect treatment by diet which

need not be any doubt as to its diagnosis in the great majority of instances. It never begins before the fifth month of pregnancy and not often before the sixth. It is associated with a rising diastolic pressure and yet does not lead to nitrogen retention, not even when the urine "boils solid" and there are signs in the sediment of a fatty degeneration of the tubule cells. When the uterus is emptied the pressure returns to normal and the signs of a renal lesion disappear. No one but an obstetrician can afford to say anything about its management, for that requires great experience and a detailed knowledge of the particular circumstances in each case. It is true that, from the standpoint of treatment, the renal lesion is unimportant, but it does not seem to the ordinary medical man that clarity and decision are forwarded by the complexity of the accounts given in the obstetrical literature as to the rôle played by the kidney. There is much use of the phrase "low reserve kidney," a concept that seems to express little more than confusion and indecision. It is a category of convenience under which may be ranged all those renal lesions met with in pregnancy that the obstetrician does not understand. This would not be important if it did not indirectly strengthen the hold of what may turn out to be only a myth, the idea that pregnancy imposes what is spoken of as a "strain" on the kidney, a strain that is supposed to bring to light these deficiencies in "reserve." No one can afford to be dogmatic on this subject, but if by strain is meant increased osmotic work by the kidney, then its existence can be categorically denied. When the protein consumption remains constant, the osmotic work of the kidney during pregnancy is a little less than usual because amino-acids whose nitrogen would otherwise appear in the urine as urea are utilized to build the embryo, uterus, and placenta. In rats on a constant diet the kidney becomes a little smaller during pregnancy. If there is any strain, in the sense of increased work, it falls not on the kidney but on the liver, in which we find a remarkable increase in size as measured by its protein content (46). On this account it would seem to be worth while to break down "low reserve kidney" into its component parts. Within this category there may be examples of all the proteinurias we are trying to classify, and it may be that pregnancy does nothing to accentuate them but is merely the occasion that leads to their discovery In any event, as far as our limited experience goes, there is no special difficulty in the diagnosis of the nature and extent of a renal lesion during pregnancy. As far as we can see, it produces no qualitative change in the characteristic features of such diseases as glomerular nephritis, chronic pyelonephritis, or polycystic kidneys. A number of our patients with glomerular nephritis in the latent and even in the degenerative stage have had normal gestations and now have healthy

babies. There is no instance in which we can be sure that the renal lesion interfered with pregnancy. There is no evidence that any of them have been harmed by pregnancy. We have had a similar experience in patients with chronic pyelonephritis and polycystic kidneys. The number of our cases and the number reported in the literature is far too small to warrant any conclusion. We may have been fortunate. We mention this experience only because it supports the general evidence that pregnancy need impose no additional burden of work on the kidneys, and we are not saying that in other not yet comprehended ways pregnancy may not sometimes lead to renal catastrophy in patients with pre-existing renal lesions. The whole question is one that calls for further observation and experiment on animals.

ABNORMALITIES IN PLASMA PROTEIN FORMATION

We have never been able to make a diagnosis of this disease on first seeing the patient. We have always supposed we were dealing with the degenerative stage of glomerular nephritis and have based our therapeutics on this supposition. In the nineteen cases we summarize here, we have, after many years of observation, come to recognize our error. Although we are at last confident these patients did not have glomerular nephritis, we are not equally certain that our present diagnosis of tubule degeneration caused by a defect in plasma protein formation is correct. It is, in fact, a hypothesis rather than a diagnosis, and a question mark is placed after the title.

The essential data obtained when these patients were first seen is given in Table 25. A detailed analysis of a recent case, not included in this series, has been given elsewhere (47).

The uniformity in their histories is apparent, as are also their normal levels of blood pressure and blood urea concentrations. Their plasma was often lipemic. They were not anemic. Edema was the single physical anomaly, and this was invariably associated with a serum protein concentration of less than 5 gm per 100 cc. Very often there were no great numbers of casts. The great majority were hyaline casts containing fat droplets. The number of cells that might be tubule cells was always greater than normal, and some of them contained fat. Protein excretion varied from less than 1 gm to over 18 gm per 24 hr. The only unusual observation was that in most of these patients the rate of red cell excretion was within normal limits and that, in the few instances in which abnormal numbers were found, immediately succeeding counts showed few red cells or none. In this, however, there is nothing decisive. Occasionally we see constant hematuria gradually diminish or even, for a time, disappear as patients with glomerular nephritis pass from the

an opportunity to observe the end. The final outcome in all these patients is given in Table 26.

TABLE 26

NAME	DURATION OF OBSERVATION	FINAL OUTCOME
B. H.	15 yr	Edema and proteinuria found Oct, 1923 Both went in the autumn of 1924, but proteinuria and later edema reappeared in 1925 and continued until Oct, 1925. No recurrence of either edema or proteinuria up to 1938.
T. D.	12 yr	Edema and proteinuria observed in 1928. There appears to have been a complete recession until 1931 when these symptoms reappeared and did not clear until 1935. No edema since. In 1940 urine was almost normal.
W. H.	8 yr	Edema and proteinuria found in 1932. Edema disappeared but returned in 1933 Six months later both edema and proteinuria went. Well in 1941.
D W.	8 yr	Edema first appeared in 1932 and lasted for 2 months. With its disap- [illegible] that to 1941.
P. L.	3 yr	Edema and proteinuria lasted for less than a month in 1935, and both disappeared Both returned in 1938. The edema quickly went, but the proteinuria did not disappear until 1940.
T. C.	17 yr	[illegible] 1925. Edema went 1 yr later but [illegible] edema.
G B.	7 yr	Edema and proteinuria developed in 1923 The edema disappeared in 1926 A slight proteinuria was still present in 1928 but by 1931 had entirely gone.
F. T.	16 yr	In 1922 edema and proteinuria were found The edema went late in 1923, but a slight proteinuria persisted until 1931 Was entirely well in 1938.
M. P.	8 yr	Edema and proteinuria appeared in 1933 and continued throughout 1934. In 1935 all symptoms disappeared. No abnormality found in 1941.
M. B.	17 yr	Edema and proteinuria first found in 1922 The edema disappeared during 1923, but a slight proteinuria persisted through 1924 By 1939 no abnormality could be found
E. B.	7 yr	Edema and proteinuria appeared in 1925 and continued until 1926 By 1927 there was no longer any proteinuria No recurrence up to 1932.
A. C.	5 yr	Edema and proteinuria found in 1926 The edema persisted for 1 yr, and the proteinuria almost but not quite disappeared 3 months later, though very low rates, with no signs of a renal lesion persisted up to 1930
J A.	3 mth	Edema and proteinuria seen in Mar, 1933 The edema varied considerably but never entirely disappeared In Nov, 1933 acute abdominal pain developed He died a few days later, probably of peritonitis.
P. N.	16 yr	Edema and proteinuria found in Oct, 1924 Edema lasted until Jan, [illegible] 1941
P. H.	3 yr	[illegible] peared
S. H.	2 yr	Edema and proteinuria appeared in Mar, 1932 and very suddenly disappeared in Nov., 1932.

TABLE 26 (Continued)

NAME	DURATION OF OBSERVATION	FINAL OUTCOME
O E.	5 mth	Died of starvation 10 months after the onset of edema and proteinuria. It was necessary to remove, at frequent intervals, more than his body weight of milky fluid from the abdominal and pleural cavities. Postmortem suggested obstruction of lacteal duct.
M. P.	6 mth	Died of carbon monoxide poisoning 15 months after her first attack of edema and proteinuria A month after she was first seen the edema disappeared and the urine was said to be protein free But shortly afterward these symptoms recurred and were present when she was last heard from, 5 months before her death. Postmortem.
D R.	4 mth	Died of cardiac failure 5 months after an unexplained edema and proteinuria were found A moderate hypertension was present (60 yr old), but during the first 3 months there were no signs of cardiac disability. Postmortem.

This outcome is not the end of glomerular nephritis, which moves toward total renal destruction or, when it heals, comes to its close by slow degrees over a span of many months or years In contradistinction, in this condition we may have an extremely rapid recovery A patient who is edematous and has a pronounced degenerative lesion, returning a month later for examination, may be found to be delivered of all these symptoms and wholly normal. Yet no external circumstance changed. He has not recovered from any infection, there has been no alteration in his diet or in any environmental condition It is as though some internal disharmony had been removed, some lost balance righted. Figure 25 shows how suddenly this may happen. An even more dramatic instance of a sudden disappearance of symptoms is the case of J. H. On November 14 he had 23.6 gm of protein in his 24-hr urine, with casts and many tubule cells. On his next visit on November 26 the urine contained only 0 1 gm of protein and thereafter all signs of a renal lesion have been absent.

With the exception of the three who died while the disease was in progress, all of these nineteen patients have been free from symptoms for many years. It begins to appear that they have made a permanent recovery. One of this series died of peritonitis while far in the country, and no postmortem examination was made. There are only two patients who seemed to belong to this group in whom a histological examination of the kidneys was made. These cases have been described in detail elsewhere (48). There was no glomerulitis, only the granular and fatty degeneration of the tubules which was indicated by an examination of the urine, and no structural change in other organs that could be related to their symptoms Pathology still leaves us with a question. It seems to say that the cause is not in the kidney or in any gross anatomical defect elsewhere in the body, and that the underlying conditions responsible for

as an explanation. We therefore predicate a decrease in the rate of plasma protein formation or an increase in rate of plasma protein catabolism.

It is obviously premature to ascribe a disease to a defect in a process whose successive steps physiologists and biochemists have not yet even roughly defined. Nevertheless, having embarked on this speculation, it is necessary to go further. When an electric current is passed through serum, the components of the protein complex separate because they move at different rates. When the serum of these patients is treated in this manner, it is found that some of the protein fractions of normal serum are present in greatly diminished quantity, and that the rates of speed are altered so that a grossly abnormal electrophoretic pattern is obtained. The lipemia may be a result of the decrease or absence of certain protein elements between whose layers fatty acid molecules usually lie recessed. We may suppose that these proteins carry the fat in molecular dispersion and obviate their coalescence into droplets. Lipemia may thus be a manifestation of an inadequate transport system analagous to a traffic jam on the road between the gastrointestinal tract and the tissues. We believe, furthermore, that the lipemia is the reason for the fatty infiltration of the tubule cells. The minute droplets of fat squeeze through the glomerular membrane and, being retrieved by the tubule cells, produce the fatty kidney. The lowering of the plasma protein concentration and the consequent edema might be due to a sharp reduction in the rate at which protein is formed relative to the rate at which it is destroyed. However, the proteinuria is still left unexplained. It develops so suddenly that a qualitative defect in the sort of protein produced is suggested: the formation of small molecules which pass the glomerular filter in unusual concentration or which, though of normal size, are so deformed that they cannot be digested by the tubule cells. This would account for a rapid filling of the tubule cells with phagocytosed protein, the development of the hyaline droplets the pathologists find in these cells, and the appearance of the unreabsorbed protein we measure in the urine.

All this may be true, but even so we would have no complete diagnosis. What are the conditions that induce the quantitative and qualitative defects in plasma protein formation or disintegration we hypothecate? How can we restore the lost level of plasma protein concentration?

DECREASE IN THE BLOOD SUPPLY TO THE KIDNEY

The kidney of the rat has what seems to us a surprising capacity for recovery from complete deprivation of all its blood supply. When we put spring forceps on the pedicle of a single remaining kidney, we found

that none of our rats died later from uremia unless the occlusion had been maintained for more than 1½ hr. To us this makes it seem likely that in man the extreme reduction in renal blood flow that is known to occur in shock might have to continue for an unusually long time before the anoxia would induce a wholly irreversible renal lesion. But even though it does not last so long, any pronounced decrease in blood supply damages the kidney. We think it is probable that special clinical situations arise in which final success or failure in the treatment of shock may be dependent on the selection of therapeutic measures for the reconstitution of a normal circulation that do not overburden the kidney (49). We may anticipate further information on this question when the experiences in the war are recounted. Apart from shock we have some as yet inconclusive clinical evidence that anuria or extreme oliguria may sometimes be caused by an almost complete closure of the afferent glomerular arterioles. What is needed now is experimental work on animals from which might be derived simple, clinical methods for the recognition of such situations. (See Addendum on p. 178.)

NEOPLASTIC DISEASE IN THE KIDNEY

We have seen patients with leukemia in whom proteinuria was the first sign of abnormality that was observed. We have seen proteinuria in Hodgkin's disease disappear after x-ray treatment. But for a clinic concerned with renal disease the most important member of this group is multiple myeloma. This is a strange and interesting disease that is hard to classify. We put it under this heading though it is doubtful whether there is any considerable infiltration of the kidney with plasma cells at the time the diagnosis is usually made. There are three clinical observations that lead to its recognition. The one that gives the diagnosis with certainty is the finding of Bence-Jones' protein in the urine; a less common sign is the finding of a very high serum protein concentration; and the latest sign of all is the revelation by x-ray of characteristic bone lesions. But any one or all of these signs may be absent and yet the patient may be dying of myeloma. We cannot even learn the frequency of this disease from postmortem records, for unless the clinician gives the pathologist the idea that it is a possibility, the usual examination may fail to reveal its existence.

When it occurs, the finding of Bence-Jones' protein is unequivocal evidence of myeloma. But there is some confusion on this point because when the methods given in the textbooks are used there may be formed, as an artefact, a small amount of protein that behaves like Bence-Jones' protein, and as a consequence it has been reported that it may be found in many diseases. When the procedures recommended by Snap-

of epithelial cell excretion that indicate a considerable increase in the death rate of tubule cells. Orthostatic albuminuria is thus not a "pure proteinuria." Doubtless there exists an anomaly characterized solely by loss of protein in the urine, without any renal lesion whatsoever. That would arise from a defect of the specific mechanism used by the tubule cells in reabsorbing protein from the glomerular filtrate. This condition would be the protein analogue of renal glycosuria. But in orthostatic albuminuria there is a renal lesion, and in the more pronounced examples this fact can be easily demonstrated.

When the possibility of the existence of orthostatic albuminuria arises, the patient is given five bottles. He is asked to void and discard urine at 8 A.M. when he rises from bed, and to collect urine at 12 noon, 4 P.M., 8 P.M., 12 midnight, and at 8 A.M. on the morning of the next day. In order that the urine may be sufficiently concentrated, he is instructed, after taking his ordinary breakfast, to abstain from fluids of any sort until all the specimens have been collected. In order that the conditions that induce proteinuria may be determined, he changes them from period to period. During the first period he is up and around engaged in his usual day's work; in the second period he runs, swims, plays tennis, or skates to the point of exhaustion; in the third period he lies down; in the fourth period he is again up and around; and during the last period he is asleep in bed. When there is some reason to suspect that lordotic positions or immobility in the erect posture are determining factors, special instructions are given. The general purpose of the examination is to define the external conditions that induce the urinary abnormalities, and to accomplish this no one set of routine instructions will suffice.

The patient we have selected as an example of orthostatic albuminuria was an 18-yr-old student in whose urine protein had been found on several occasions during the past 4 yr. He came because he wanted to know whether it would do him any harm to try out for the track team. No abnormalities were found on physical examination. The night urine obtained after abstention from fluids had a specific gravity of 1.036 and was equivalent to a 24-hr volume of 456 cc. It contained a very few hyaline casts (4,200 per 24 hr), no red cells, and 1,700,000 epithelial cells. The 24-hr rate of protein excretion was 0.07 gm, a quantity that, with the method we then used, was not definitely abnormal. Another similarly concentrated urine contained no casts, no red blood cells, and 0.3 gm of protein in 24 hr. These observations excluded the possibility of a latent glomerular nephritis, but they gave no explanation of the fact that at times very definitely abnormal amounts of protein had been found.

curious coincidence of a continuously high blood urea concentration with an almost normal blood-pressure. But no one was able to feel the kidneys and the diagnosis was made not by clinicians but by the pathologist who, on entering the postmortem room and observing large, oval protuberances in the relaxed flanks of his subject, made the remark, "Well, I see we have a case of polycystic kidneys today."

There is nothing pathognomonic in the results of the clinical methods we have described. Small numbers of hyaline casts are sometimes found in those who are not already uremic; and in those who are, renal failure casts are often seen. The number of epithelial cells is usually far above normal even when there is no frank pyuria. Red cells may be absent or present in any number up to gross hematuria. Protein is always found, and here is the only point that may be called even suggestive, for in a few cases in which observations were made over a long period of time there now and then came a day on which the proteinuria, which was running fairly constantly at a level of less than 1 gm in 24 hr, would rise to quantities five to ten times greater than the usual level.

This is a disease in which dietetic treatment is important, and perhaps not only in those patients who are already uremic. For them the treatment of the terminal stage of glomerular nephritis applies. But in the earlier stages, even though these patients are the victims of a progressive disease, it is possible we might be able to slow down the rate of development by dietetic measures that reduce the blood flow through the kidney. It is this possibility that makes important the question of what shall be done with the children of these patients. If there were no hope, it would certainly be kind to leave them alone. Since hope exists, we have to try to bring about a reduction in the osmotic work of their kidneys if we can do it without making them anxious.

DISEASES OF THE RENAL ARTERIES

Under this vague and noncommital title we place disseminated lupus, periarteritis, and symmetrical necrosis of the cortex. We mention the first two of these diseases because sometimes, toward their close, the lesions in the kidney produce not only proteinuria but urinary sediment changes that are striking and characteristic. Krupp (52) has described what we have come to call the "telescoped" sediment, because it combines the blood-casts of the initial stage, the fatty casts and fatty tubule cells of the degenerative stage, and the broad renal failure casts of the terminal stage of glomerular nephritis all together, at the same time, in one sediment.

Symmetrical necrosis of the cortex was the diagnosis reached in four patients with anuria. Two of them were women seen soon after delivery.

In the two men the anuria was preceded by a fever, induced by catheterization in one and associated with vomiting and diarrhea in the other. All of them recovered. (See Addendum on p 178.) The diagnosis is based on the singular course of the uremia which followed the anuria. In Figure 29 we reproduce some of the observations made in one of these patients.

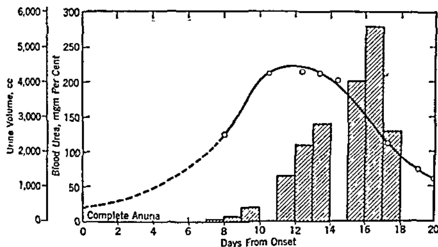


Fig. 29. The slow recovery from uremia in symmetrical necrosis of the cortex.

The essential feature of this uremia is the slow fall in the blood urea concentration in spite of the excretion of large volumes of urine. When urine flow is re-established in a normal kidney whose function has been temporarily stopped, as in the anuria occasionally seen with ureteral stone, the fall in blood urea concentration is very abrupt. A slow fall is evidence that the total amount of functioning renal tissue is greatly reduced. In this disease the circulation through large sections of the cortex is stopped. As the sections that are spared begin to recover from the effects of the general circulatory disorganization within the kidney, they are at first quantitatively insufficient to do more than plateau the hitherto rising blood urea concentration, and only slowly and by virtue of compensatory hypertrophy are they able to bring the concentration to normal levels. The urine obtained during this slow recovery is extremely dilute. It contains no casts, but there are large numbers of epithelial cells and tens or hundreds of millions of red blood-cells. The protein concentration may be high but because of the small urine volume the rate of excretion is less than 1 gm per 24-hr and does not rise much above 2 gm even when the volume becomes larger.

In every anuria the first possibility to be excluded is a mechanical obstruction. Once that has been done, symmetrical necrosis should be

remembered whenever no other obvious cause is present, especially if the patient has a rapid sedimentation rate. If we make this tentative diagnosis, we have at the same time chosen the treatment. There is no surgical or mechanical manipulation that can foster the growth of the remnants of renal tissue. The remaining nephrons are hard-pressed and grossly overworked. This is an emergency that warrants an all-out reduction in the osmotic work of the kidney, analogous to that recommended in the initial stage of glomerular nephritis.

HYPERTENSION

No one of the many conditions often ranged under the name Bright's disease is more prevalent or more difficult to treat than what we are accustomed to call "essential hypertension." So, although we engaged to deal in a very summary manner with diseases other than glomerular nephritis, we ask in this case some slight indulgence because, unless we try to get a little behind the presenting signs and symptoms, nothing specific can be said about either diagnosis or treatment.

The hypertension we call "essential" is an abnormally high level of diastolic pressure in the systemic circulation. This excludes the diseases in which only the systolic pressure is too high, as, for instance, hyperthyroidism or the systolic hypertension we find when the large arteries have lost much of their usual elasticity. In order to make this criterion a little more definite we shall define essential hypertension as a rise in diastolic pressure to 100 mm of mercury or over, and require that this level of pressure shall, by and large, be maintained at or above 100 mm under any ordinary daytime conditions. We thus eliminate the very many clinical states in which the diastolic rise is only transitory and specifically conditioned.[1]

This is the end of what everyone can agree is positive about this condition; the rest is a series of negations. Patients with increased diastolic pressures who have glomerular nephritis, chronic pyelonephritis, polycystic kidneys, pheochromocytomas, Kimmelsteil Wilson disease, coarctation of the aorta, or brain tumors are not instances of essential hypertension. The people we are talking about are those in whom we fail to find evidences of any abnormality that can reasonably be regarded as giving rise to hypertension.

We believe that the rise in diastolic pressure must be caused by a generalized constriction of the arterioles of the systemic circulation, although we can see the constriction only in the retinal arterioles. The

[1] If we make this requirement there is good reason to believe that we exclude the first stages of essential hypertension itself. However, at that time there is no proteinuria, so that the question of the differentiation from glomerular nephritis—the question we are now discussing—does not arise.

rise in systolic pressure, without which the blood supply to the tissues would not be maintained, is a secondary phenomenon. The sequence of abnormalities that develop later can be interpreted as a consequence of the arteriolar constriction. Although it is proper for pathologists to describe the last stages of this condition in terms of the location and degree of arterial disease, it is right that clinicians, who see these patients before there is any arteriosclerosis, should classify and arrange their observations in accordance with the levels of diastolic pressure they measure. This is more than a symptom; it is the cause of the pathological changes in the arteries and the reason for the dangers to which our patients are subjected.

Eighty-four patients have been followed to the end. Of this number 70% were men, and 30% were women. When they were first seen their diastolic pressures ranged from 100 to 190, with an average of 147. The distribution is given in Figure 30

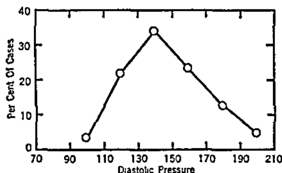


Fig 30. Diastolic pressure in "essential" hypertension when first seen.

It is evident from this high average level of pressure that our experience is not with an average group of hypertensives. We had referred to us a group in which there were a preponderant number of patients with an unusually intense arteriolar constriction. We therefore cannot speak of essential hypertension, in general, but only of the condition as it presents itself in its most severe and fulminating form. This does not mean that the patients we saw were generally those who had had hypertension for a long time and had thus gradually come to have very high pressures. Figure 31 shows that the higher the diastolic level at the time the patients were first seen the shorter, as a rule, was the total duration of symptoms, i.e., the period between the time when they first were told they had hypertension or the time at which they began to suffer from symptoms and the time at which they died.

The time of onset of symptoms is not, of course, the time of the onset

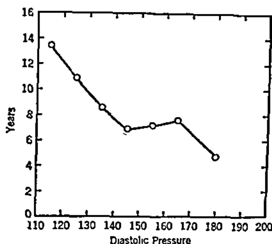


Fig 31 Total duration of symptoms and diastolic pressure when first seen

of the disease. The discovery of the condition is often accidental, for at first it is a symptomless disease. The hypertension itself comes so gradually and with such intermittence that it is hard to say when it begins. There are those who believe there is a genetic factor involved or that characteristic "personality defects" are constantly present, but, however that may be, the evidence begins to accumulate that the earliest stage of hypertension begins with very transient elevations of pressure long before a more or less permanent diastolic increase is established. So the age at origin cannot be defined with any precision. Only the age at death is certain (Figure 32).

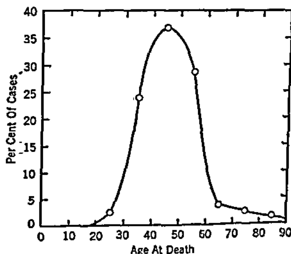


Fig. 32. Age at death in "essential" hypertension.

When we arrange the ages of these patients at death in correspondence with the level of diastolic pressure observed when they were first seen, we find that when the diastolic pressure was 115 they died at just over 60 yr of age, when the diastolic was 145 they died at 45 yr, and when it was 175 the average age at death was 40 yr (Figure 33).

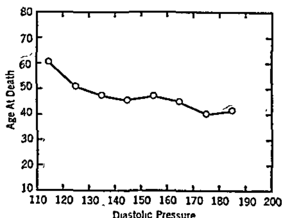


Fig 33 Age at death and diastolic pressure when first seen.

If we plot the duration of life from their first visit against the first diastolic pressure readings we measured, we get the curve shown in Figure 34, from which we may conclude that patients whose diastolic pressure is over 150 will most usually die within 2 yr of the time we see them.

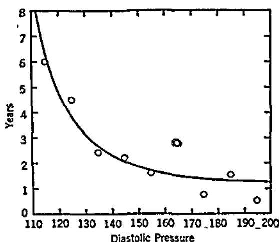


Fig 34. Years of life from time of first observation to death, in relation to diastolic pressure when first seen.

reduction in the blood-pressure level. But in the out-patient department we have not been able to distinguish between the physical and the psychological effects. We believe both are involved, and that such efficacy as the method possesses is a consequence of their combination. In this particular group of patients, about a month after the treatment was begun, the effect on the average blood-pressure levels is shown in *Figures 37 and 38.*

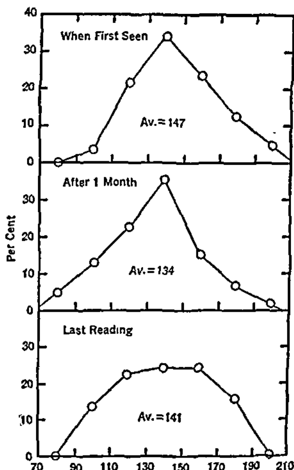


Fig. 38. Diastolic pressure in "essential" hypertension.

This was not a great effect, nor was it permanent. But this slight decrease in pressure was accompanied by a much greater degree of subjective improvement. *The effect was not uniform throughout the group* but tended to vary inversely as the diastolic level. In those whose diastolic pressure was always 150 or over there was often no change in pressure, and even the symptomatic betterment was sometimes *doubtful*

or absent. For these patients we recommended splanchnectomy when their symptoms became intolerable or when the retinitis began to threaten the loss of reading vision. However successful we often are in the relief of symptoms in lesser grades of hypertension, these cases show most clearly that our treatment in severe cases was merely palliative. We cannot escape the extension of this conclusion to all patients with essential hypertension for there is no adequate clinical evidence to warrant the supposition that "malignant hypertension" is a separate disease or more than an extreme degree of essential hypertension.

BACTERIA GROWING IN THE KIDNEY

We select two examples of this group—the first a specific infection of the kidney by the tubercle bacillus, and the second that slow disorganization of the renal architecture induced by a multiplicity of bacteria which we call chronic pyelonephritis

Renal tuberculosis—The early diagnosis of renal tuberculosis is a responsibility that falls, as a rule, on the physician rather than on the surgeon, and it is a serious responsibility because of the harm that may be done if there is delay in reaching a diagnosis. We allude here to this disease because the associated proteinuria sometimes leads to a mistaken diagnosis of nephritis. This was the case in the patient from whom the data given in Table 28 were derived. He was a flier in a foreign army who had been treated for Bright's disease and was finally discharged with that diagnosis.

TABLE 28

PROTEINURIA AND SEDIMENT IN RENAL TUBERCULOSIS

YEAR	MONTH	PROTEIN	RED BLOOD-CELLS	WHITE AND EPITHELIAL CELLS	NOTES
		mgm per 24 hr	millions per 24 hr	millions per 24 hr	
1944	July	1800	120	1056	Guinea pig positive
/	Aug				Right nephrectomy
/	Oct.	1820			Guinea pig positive
/	Oct.	713			
/	Dec.	227	1200	84	Guinea pig positive
1945	Apr.	67	90	9	
/	May	134	42	7	
/	Aug	98	39	1	Guinea pig negative
/	Sept.	105			
1946	Feb.	86	69	2	Guinea pig negative
/	Apr	167	25	2	Guinea pig negative
/	May	49	4	4	Guinea pig negative

The microscopic hematuria and the minimal proteinuria that in Table 28 are shown to continue long after the guinea-pig injection tests became negative may reasonably be taken as indications that the renal

reduction in the blood-pressure level. But in the out-patient department we have not been able to distinguish between the physical and the psychological effects. We believe both are involved, and that such efficacy as the method possesses is a consequence of their combination. In this particular group of patients, about a month after the treatment was begun, the effect on the average blood-pressure levels is shown in Figures 37 and 38.

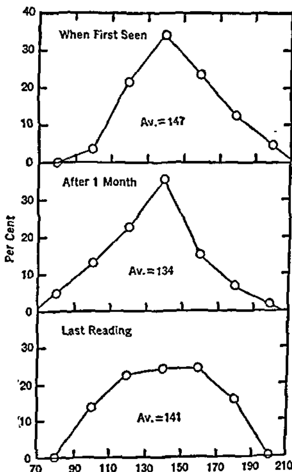


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The microscopic hematuria and the minimal proteinuria that in Table 28 are shown to continue long after the guinea pig injection tests became negative may reasonably be taken as indications that the renal

lesion is not yet quite healed. But we do not think that this supposition should be used as a reason for the imposition of anything approaching complete bodily inactivity. In this instance there is no sign of pulmonary tuberculosis. There would be no question about the value of avoiding muscular exertion if there were. But moderate exercise does not increase the blood flow through the kidney, and it has no direct effect on its work. What we know is that a decrease in osmotic work is associated with a decrease in the rate of blood supply to the kidney, and so it seems not unreasonable to suppose that a diet with no more than an adequate amount of protein and plenty of fluids may be one factor that favors the healing of a tuberculous renal lesion.

Chronic pyelonephritis—Twenty-two is not a great number of patients to have followed to the end. The number, of course, grossly underestimates the frequency of the condition in out-patient practice. But for a long time our primary interest was in diagnosis, and we sent these patients elsewhere for treatment. It is only during the last 10 yr or so that we have come to understand that patients with chronic pyelonephritis need medical care quite as much as the glomerular nephritics whose kidneys are growing small.

In the majority of these patients, diagnosis is not a problem. In 34% of this series it had already been established by the surgical removal of one kidney. In another 34%, the surgeons had made the diagnosis on the basis of retrograde pyelograms, and in many of these patients the ureters had been dilated or the prostate removed. They were patients with long-standing gross pyuria. There remains a group who come first to the physician rather than to the surgeon. Their history sometimes makes no reference to the urinary tract. Their complaints are varied and in general are the results of uremia, anemia, and hypertension. Their urine is clear, and it is obvious at a glance that they have no gross pyuria. They are patients in whom a symptomless pyelonephritis has for many years been slowly destroying most of the kidney substance. When we first see them, the acute inflammation has burned itself out. The urine from their scarred, fibrous kidneys contains no very obvious evidence of the nature of the lesion. *These, only*, are the chronic pyelonephritics in whom diagnosis should be discussed. In Tables 29 and 30 we give some of the essential clinical data. In Table 30 the cases are arranged in order of difficulty in diagnosis. In the last two, the diagnosis was given to us, since one kidney had been removed many years before, but we include them because they also were "inactive" chronic pyelonephritics.

When we see how high was the level of blood urea concentration of these patients at their first visit, and when we note that the "duration of

TABLE 29

"INACTIVE" CHRONIC PYELONEPHRITIS

CLINICAL LABORATORY FINDINGS

		blood		urine—24-hr rates of excretion				
number	name	urea when first seen mgm per 100 cc	red cell volume when first seen % of normal	volume cc	casts, millions	red cells when first seen, millions	epithelial or white blood-cells when first seen, millions	protein gm
1	C. T. L.	420	36	1104	0.0	8.0	36.0	1.94
2	S. K.	72	78	846	0.14	3.0	210.0	2.90
3	M. A.	197	65	824	0.0	0.4	1.2	0.77
4	A. L. N.	49	71	1820	0.0	0.5	10.0	3.81
5	B. W	131	78	2940	0.0	2.0	12.0	4.08
6	G. W	68	81	1204	0.0	0.0	12.0	3.23
7	B M. B.	125	80	2340	0.0	9.0	73.0	2.59
8	G C	245	45	660	0.0	5.0	5.0	3.00
9	V H	100	70	1208	0.0	0.2	4.0	1.35

observation" indicates that some of them went on living for years, we have an index of the very slow progression of this renal lesion. Any prolonged uremic or suburemic state should in itself suggest the possibility of an inactive chronic pyelonephritis. The actual rate of progression of the renal lesion is, in reality, even slower than these facts suggest because, although the cause of death is in all cases given as uremia, it was not alone the almost complete destruction of what few nephrons remained that precipitated the last irreversible renal failure. The final collapse is often initiated by what seems to be a brain edema secondary to an extreme arteriolar constriction, as indicated by a very high diastolic pressure with choked disks and, in three of our series, by convulsions.

The clinical laboratory data in Table 29 give the clue to the diagnosis, though mainly by exclusion. In the table we have copied out the first urine counts. It will be noted that though the urine looks clear the number of epithelial cells and pus cells is usually far above normal. The number alone, however, does not always differ from what is often seen in the terminal stage of a glomerular nephritis; it is the fact that most of the cells seem to be pus cells rather than tubule cells that should raise suspicion. This, unfortunately, is one of those qualitative and uncertain judgments which must always be regarded with suspicion. Nevertheless, it begins to mean something if, in subsequent examinations, counts of 100,000,000 or 200,000,000 "epithelial and white blood-cells" are found every now and then. It is evident then, from the number alone, that most of these cells must be white blood rather than tubule cells For, however inactive the lesion, it is not wholly healed, and every now and then it lights again. Sometimes, too, we find a bacteriuria, usually transient, though this is not seen in many patients

To us the most interesting and perhaps the most constant sign in the

TABLE 30

"INACTIVE" CHRONIC PYELONEPHRITIS

ARRANGED IN ORDER OF DIFFICULTY IN DIAGNOSIS

number	name	sex	age at death	apparent duration of symptoms	duration of observation	cause of death	post mortem	main clinical reason for diagnosis	blood-pressure first systolic	blood-pressure first diastolic	blood-pressure last systolic	blood-pressure last diastolic	retinitis	convulsions
1	C. T. L.	M	13	*2 yr*	*4 months*	*Uremia*	+	*Clinical* course and urine	140	100	150	120	0	0
2	S. K.	F	35	16 yr	2½ yr	Uremia	+	Clinical course and urine	150	100	180	120	+	+
3	M. A.	F	42	13 yr	1¼ yr	Uremia	0	Clinical course and urine	180	115	150	100	0	0
4	A. L. N.	F	42	11 yr	7½ yr	Uremia	0	Clinical course after pregnancy, pyelonephritis	120	90	150	100	0	0
5	B. W.	F	32	30 yr	1½ yr	Uremia	0	Childhood pyelonephritis	150	100	160	120	0	0
6	G. W.	F	38	10 yr	2 yr	Uremia	0	X-ray difference in size of kidneys	200	135	200	150	+	+
7	B. M. B.	F	42	19 yr	2 yr	Uremia	0	X-ray *difference in size of* kidneys	*165*	*100*	*175*	100	0	0
8	G. C.	F	24	20 yr	2 months	Uremia	+	One pyelonephritic kidney removed	135	90	220	130	+	+
9	V. H.	F	62	36 yr	5 yr	Uremia	+	One pyelonephritic kidney removed	220	*140*	*210*	130	+	0

TABLE 31

"ACTIVE" CHRONIC PYELONEPHRITIS

CLINICAL LABORATORY FINDINGS

			urine—24-hr rates of excretion				
number	name	blood urea when first seen, mgm per 100 cc	volume cc	casts millions	red cells when first seen, millions	epithelial or white blood cells when first seen, millions	protein gm
10	B. B	86	1300	0.0	19,000.0	1250	3.27
11	R. H.	61	2010	0.0	0.5	240	1.50
12	C. C.	69	1044	0.0	0.0	2000	2.52
13	J. C.	288	1152	0.1	9.0	400	3.48
14	B. M.	74	2160	0.0	198.0	1150	1.60
15	I. McG.	216	1132	0.0	0.0	2000	6.80
16	J. R.	170	4260	0.0	0.0	2000	
17	H. W.	232	1540	0.0	0.0	2000	1.50
18	J. F.	111	2220	0.0	0.0	825	2.58
19	A. McM.	70	892	0.0	15.0	118	1.94
20	P. H.	95	1760	0.9	0.0	1670	1.76
21	E. L.	85	2012	0.1	21.0	218	1.56
22	H. L.	58	1078	0.0	82.0	660	0.70

ject to all the reservations that clinical experience has taught us to make with respect to such uncontrolled observations in the therapeutic field. In the end, the treatment was ineffective. In all these patients the blood urea, hypertension, and proteinuria subsequently rose, and they died. This failure, we think, was due more to a progressive arteriolar constriction than to the renal lesion itself.

There is another method of treatment that is preventive rather than curative. We owe it to Helmholtz (56) who pointed out how even small doses of sulfa drugs will stop the growth of certain organisms in the urine. These chemicals are almost wholly excreted through the kidney, which concentrates them from the blood. If we give 100 mgm of sulfathiazole four times a day, there will always be sulfathiazole in the urine and every 24 hr about 320 mgm will be excreted. If a liter of urine is formed there will be over 30 mgm of sulfathiazole per 100 cc of urine, and, even if the 24 hr urine volume is 3 liters, there will be 10 mgm per 100 cc of urine. During the last 6 yr we have asked all our patients with chronic pyelonephritis to take a 100-mgm tablet of sulfathiazole with a glass of water before breakfast, at lunch, at dinner, and just before going to bed. They continue to do this without interruption as part of their daily routine. Since that time, it happens that there has been no recurrence of the fever and gross pyuria from which some of them used to suffer now and then. There has been no indication that these minute quantities have done them any harm, though two previously sensitized patients could not continue because they developed signs of trouble after the first few doses.

This, of course, is at best a way of preventing the growth of certain bacteria in the urine. There is no dose of sulfa drugs it is practical to give that will sterilize the kidney. But our experience begins to make us think that infection of the urine may be a not unimportant factor in the progression of the renal lesion in chronic pyelonephritis, and that we ought to do something to prevent these reiterated episodes in which the urine becomes like an overgrown broth culture of organisms. There is almost certainly obstruction to the outflow of urine in this disease. The calyces are distorted by the traction of fibrous tissue, so that it seems very likely that here and there a pooling of urine occurs. The surgeon cannot remedy this sort of intrarenal obstruction. It remains as a constant menace. Granted the proper pH of the urine and certain other conditions, organisms excreted by the kidney may enter these pools and start a local fire that may become a conflagration. For then the infected urine becomes in itself irritating and induces such an edema of the neck of the calyx that there is complete or almost complete obstruction to the outflow of urine from the collecting tubules of the whole section of nephrons

that drain into the papilla of that calyx. Then we have the situation with which we are all familiar—the patient with a high fever, tenderness below the last rib on one side, and a urine loaded with bacteria and pus cells. Perhaps the irregular scarring and distortion of the kidney that in the end we find in these patients is due as much to such reiterated infections of the urine as to the continued action of bacteria in the interstitial tissue. This is, at least, a therapeutically hopeful hypothesis that warrants the use of any harmless means to prevent the growth of bacteria in the urine. It is, of course, a preventive, not a curative, measure. For the latter we have to wait for observations on the effect of penicillin and streptomycin.

BACTERIA IN THE BLOOD THAT INDUCE GLOMERULITIS

The renal lesion here is only one of the manifestations of bacteremia. It is produced most frequently by the streptococcus viridans, but similar lesions are sometimes found in staphylococcal, gonococcal, and, perhaps, some pneumococcal septicemias.

Some pathologists, observing that the glomerular lesions in the acute and chronic stages of streptococcus viridans septicemia are not unlike those seen in the disease known to clinicians as glomerular nephritis, have described them under one general heading as forms of glomerular nephritis.[2] From a strictly pathological standpoint they are doubtless justified. Clinicians, however, will not use a classification based solely on the structural changes found after death. We have to prevent and treat disease in the living. In ordering our experience, the beginning of disease is in fact more important than the end because etiological knowledge sometimes leads to effective preventive action. On the other hand, we cannot be content with an etiological system of classification either, not only because the conditions that determine disease are complex and involve so many still uncomprehended reactions between external and internal factors, but principally because there is more to a disease than a beginning and an end; there is its whole development and course.

[2] See, for instance, E. T. Bell, who writes what seems to be an excellent pathological description [illegible]
Nephritis [illegible]
pathology [illegible]
taken in [illegible]
when pathologists took clinicians too seriously and were hampered in their development on that account. Nowadays there is some reason to fear that clinicians are becoming [illegible]
[illegible] product of one another.

stage we happened first to see them, we find that in most of them there is no evidence of a preceding illness of any sort. To us this means only that in a large proportion of our cases the initial stage passed unnoticed and undiagnosed. These patients came to us long after an unobserved beginning, because they were edematous or uremic or because a routine examination of the urine had revealed a proteinuria. But since we can attach no positive value to what may be only ignorance on their part, we must restrict an investigation into the nature of the preceding illness to those patients whom we actually saw in the initial stage and to those whose story of the initial stage was well documented. There were 115 such patients. They gave us the list of diseases given in Table 34.

TABLE 34

ILLNESS PRECEDING INITIAL STAGE OF GLOMERULAR NEPHRITIS IN 115 PATIENTS

	%
Tonsillitis	39
Scarlet fever	16
Operation infections 8% } Skin and subcutaneous tissue infections 7% }	15
Sinusitis, etc	12
Middle ear disease	11
Undiagnosed fevers	3
No known infection	3

This seems to us evidence that a single infection always precedes glomerular nephritis, for all these diseases may well be various forms of infection by the beta-hemolytic streptococcus. In this we only underline the conclusion toward which other observers are tending. Such diversity of opinion as still exists appears to us to be occasioned not by a difference in the stories patients with glomerular nephritis tell us but rather by the error of some bacteriologists and pathologists in confusing glomerular nephritis with the renal lesions in pneumococcal, staphylococcal, gonococcal and streptococcus viridans septicemias.

INTERVAL BETWEEN ONSET OF PRECEDING ILLNESS AND THE ONSET OF GLOMERULAR NEPHRITIS

This interval is one of the most curious characteristics of glomerular nephritis. It is not like the incubation period of an infectious disease. The tonsillitis or the scarlet fever had an incubation period, but that has passed and these diseases have run their course before glomerular nephritis begins. When it comes, there is no recrudescence of the streptococcal infection; no one can find streptococci in the kidney; in fact, there need be no streptococci left anywhere within the body, for glomerular nephritis begins at a time when the antibodies against the streptococcus are at a high concentration and the patient is pre-

sumably relatively immune. *It thus resembles the delay between the* introduction of an antigen into the body and the development of an allergic reaction. It has its most exact counterpart in the adenitis, arthritis, and myocarditis that sometimes appear after the same interval of time and which are the true analogues of glomerular nephritis. All the hope for the prevention of glomerular nephritis lies in the study of the meaning of this interval. We can speak here only of its duration, which may be as short as 3 and as long as 33 days, and has the broad distribution shown in Figure 39.

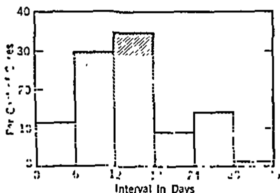


Fig. 39 Interval between the onset of the preceding illness and the onset of glomerular nephritis.

Seasonal Incidence

The general contour of the curve is determined by the seasonal incidence of tonsillitis and scarlet fever, but the summer recession is not so deep, presumably because there is no season for operations in infected areas or for streptococcal infections of the skin and subcutaneous tissues. Figure 40 shows the percentage incidence for successive 3-month intervals.

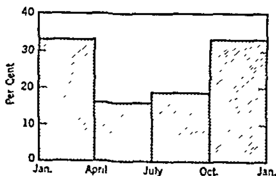


Fig 40. Seasonal incidence in the onset of glomerular nephritis.

Age Distribution at Onset

Of all our glomerular nephritics, 70% were between 5 and 20 yr of age and 39% were between 5 and 10 yr old when the disease began. But no age is immune. We have seen the initial stage develop in a 6-months-old baby and in an 87-yr-old woman. It is a disease that belongs in common to pediatrics and to internal medicine. The breadth of the distribution is shown in Figure 41.

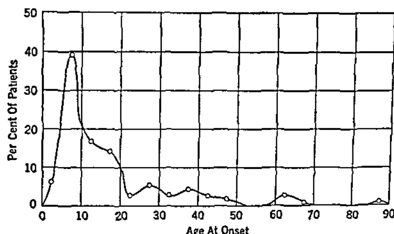


Fig 41. Age distribution of 113 patients in the initial stage of glomerular nephritis.

Sex Distribution

Of 247 patients with glomerular nephritis 68% were males and 32% females. This inequality calls for explanation, but the answer is not necessarily to be found in any unique characteristic of glomerular nephritis, for we have found the same distribution in the other renal diseases we have considered. We recapitulate these figures in Table 35.

TABLE 35

Sex Distribution in Renal Disease

DISEASE	NUMBER	PERCENTAGES males	females
Orthostatic proteinuria	54	87	13
Polycystic disease	12	92	8
Chronic pyelonephritis	21	33	67
Degeneration associated with a defect in plasma protein formation	20	65	35
Essential hypertension	84	70	30
Glomerular nephritis	247	68	32

The marked preponderance in males of orthostatic proteinuria and of polycystic disease may be related to a greater probability of failure in the perfection of the intrauterine construction of the male urinary tract.

The reversal of the usual sex incidence in chronic pyelonephritis can reasonably be ascribed to the fact that in the female the urethra is so much shorter than in the male and is thus a more accessible portal of entry for ascending infections of the urinary tract. But in renal degeneration of unknown causation, in essential hypertension, and in glomerular nephritis the reason why the incidence should include two males for every female need not be any anatomical difference between the sexes. It is part of the problem of the sex incidence of disease in general, which is discussed by Perla and Marmorsten (58).

Occurrence in More Than One Member of a Family

There are a few reports of several members of the same family having had what appears to have been glomerular nephritis, but even if all of this material were to be used there does not seem to be enough to decide whether the family incidence is greater than chance might provide. In a matter of this sort nothing is more likely to confuse the issue than the inclusion of doubtful data. It is not very uncommon to hear from patients that some other member of their family died of Bright's disease. Certainly that sort of evidence should not be accepted. We have gone to the other extreme and have only included families in whom we have followed two or more members for a considerable time and have come to be sure of the diagnosis. There have been only seven such families. We should not mention them if it were not for the curious circumstance that in five of these seven families three or more members were involved. In the first instance we came across, four children developed glomerular nephritis almost simultaneously after tonsillitis. They are all in the latent stage now, and each continues with a lesion that has quite distinctive features. In another family three brothers were found with the disease, though the onset had not been observed. One of them has since died of uremia, another is now suburemic, and the third has a relatively mild, latent lesion. Another family, also without knowledge of the time of onset, has one member we watched as he healed and three others who are still latent. There were two other families each with three members with glomerular nephritis.

Having seen five families, each with three or more instances of glomerular nephritis, it would seem highly probable, if this were due to chance alone, that we should find a larger number of families in which there were two cases. But, in fact, we have seen only two families of that sort—one with a mother and son and the other with a father and son. It is this circumstance that makes us feel that there may be an occasional family that is "predisposed" to glomerular nephritis. We mean by this more than susceptibility to infection with hemolytic strep-

tococci, for, in view of the fact that only something like 1% of patients with scarlet fever develop glomerular nephritis, this family incidence would require more than that as an explanation. At any rate, the question seems to be worth raising if only in the hope that the combined experience of others may make it one that is, beyond question, real.

Occurrence in Identical Twins

We have seen four patients with glomerular nephritis, each of whom was one of a pair of identical twins. In each instance only one of the twins had developed the disease. We think this is instructive. When we consider any hundred children with scarlet fever and begin to wonder why glomerular nephritis occurs in only about one of the hundred, the first supposition that comes to mind is that there must be some peculiarity in the victim that makes him susceptible. But finding that this particular patient seems in no outward way different from the other ninety-nine, that the conditions that surround him seem to be the same, that there is nothing unusual in the scarlet fever through which he has passed, and that there is no constant physical difference between him and the other children, we naturally suppose that this hypothetical peculiarity must lie concealed within him. The next step, perhaps remembering something about the family incidence of glomerular nephritis, is to suppose that the peculiarity consists of some subtle inherited trait, something that falls within the realm of what we rather vaguely term "constitutional." It is true there are clinicians who are striving, and not without some success, to give this term a more specific meaning, but for most of us it is still a sort of wastepaper basket in which we deposit problems we have failed to solve when they begin to bother us too much. Certainly in connection with the problem of the mechanism of the onset of glomerular nephritis we know very well that thought has stopped by the time appeal is made to constitutional factors. Now the value of the observation that in four instances of glomerular nephritis in identical twins only one of each of the pairs developed the disease lies in the fact that in these cases we cannot make use of our usual means of escape. Identical twins have identical constitutions. They are halves of one egg. They have the same chromosomes and the same cytoplasm. When the halves of this identity contract scarlet fever together and only one half develops glomerular nephritis, we cannot appeal to any chromosomal or cytoplasmic difference that existed from the instant of their inception, for in this case we know there was no such difference. That road is closed. We are forced to try to find some other way out of the impasse.

In the first instance we saw, we find two little identical twin girls

going through a mild scarlet fever together. There is every reason to assume that they were infected with the same strain of beta-hemolytic streptococcus. Their general surroundings were the same. They even slept in the same room. But only in Irvine did the urine suddenly turn brown and all those changes begin which, as years went by, made her very different from Irene and in the end led to her death by uremia. In spite of the apparent uniformity of the conditions before and during the onset of the disease, there was some determining difference. We can imagine several. As one example, Irene might have been lying under the covers and Irvine might have been sitting up while a chill wind through an open window played upon her back (59). Or, a difference in the streptococcal invasion of the tonsils in Irvine might have induced a quantitatively different antibody response. Some difference there must have been, and the certainty that it exists should provide the energy needed to find it. It might quite possibly be something we can prevent.

Clinical Facts That an Adequate Hypothesis as to the Mechanism of Onset Must Explain

The interval that elapses between the onset of the beta-hemolytic infection and the onset of the nephritis strongly suggests that an antigen antibody reaction initiates the renal lesion. We emphasize the renal lesion because of its clinical importance, but the generalized edema, the hypertension, and the frequent association with myocarditis, adenitis, and arthritis indicate that at the very beginning, at least, the effects are very widespread. Clinical evidence shows that if this is an antigen antibody reaction, it is differentiated from other clinical states in which this hypothesis is satisfactory by the circumstance that it occurs only once and never recurs. A general negative statement of this sort can, of course, never be trusted, but it is true in a large number of patients followed over long periods of time we have never seen a recurrence of the initial stage. The exacerbations so frequent in the latent stage are quite different from the onset, even when it happens that they are induced by a streptococcal infection. If the disease begins with an antigen antibody reaction we cannot account for more than the very beginning. What we observe later is not the reaction itself but only the processes of repair that follow it. This is very evident at the beginning in the rapid subsidence of the rates of protein and cell excretion and is supported by the rapid disappearance of the edema and hypertension.

It does not seem to us that the subsequent course of the disease can be accounted for on the basis of a state of continuous or recurrent reaction, though it is possible that all the aftereffects are consequences of a single, initial result of this nature. However we have no grounds for

not noticed that his urine looked like coffee; he was, of course, unaware of his hypertension, and he had not realized that his subcutaneous tissues had become "thick all over." Since there is usually no pain, no discomfort, and no malaise, it is understandable that such signs should often be overlooked. Of course, no one can prove that glomerular nephritis may not sometimes start in a way altogether different from the manner with which we are familiar. On the other hand it does seem reasonable to ask the proponents of the school of the insidious beginning to give us some evidence for their belief. As yet they have not given us any. Since, when we have seen it, glomerular nephritis has started suddenly and, though with great variation, quite distinctively, we shall continue to believe that this is true in every case until the facts show us we are wrong We shall therefore assume that 100% of our patients started on their course from a more or less typical initial stage. The second assumption is that a patient has passed through the degenerative stage, even though we do not see it, if he gives a history of a soft, pitting edema that continued for months or years and that was not associated with dyspnea on exertion. For the historical recovery of the degenerative stage we thus rely on the recollection of people, although for the initial stage we attach no weight to their forgetfulness or inattention. Under the circumstances this is justifiable, because no one could fail to notice the sort of edema that appears in the degenerative stage, and it is unlikely it could ever be forgotten. If these assumptions are granted we can chart the course taken by the disease in the manner depicted in Figure 42.

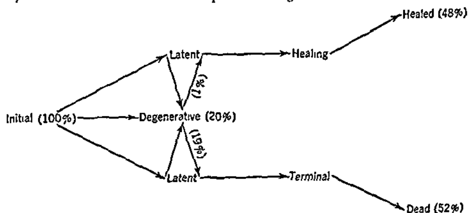


Fig. 42. The course taken by patients with glomerular nephritis.

This was the course followed by 216 patients who came to our outpatient clinic and who either entirely recovered or died of uremia. We exclude the 19% of all our cases in which death was due to intercurrent disease and also the two patients who died of cardiac dilatation in the

initial stage. Very different results would be obtained if a similar outline had been constructed from data derived from patients treated in a hospital. A much more pessimistic conclusion as to the death rate would then have been reached, and there might be no latent stage at all. Both conclusions would be statistically correct. Neither of them can claim to depict the development of the disease, though the out-patient picture is unquestionably nearer the truth. A man practicing in a stable community, if he lived long enough and looked hard enough, would reach a closer approximation. But in some measure all of us will fail to see all of a disease that runs a course so silent and stealthy. Polemics about the proportion of patients that heal or die in uremia are vain because our figures (granted that our methods are the same) will be determined by the questions we are interested in answering, the sort of patients that are referred to us, and many other local and individual factors that have nothing to do with the disease as a whole. It is worth noting, however, that most of these extraneous circumstances tend toward a too gloomy view as to the general outcome in glomerular nephritis. It is obvious, also, that we have to take account of the heavy overweighting with serious renal lesions in our group of 216 patients. Also we have to discount the significance of the high proportion who passed through the degenerative stage. Every patient who becomes edematous goes to a doctor, but it is probable that only a few of all the patients in the latent stage are seen at all.

Initial Stage

THREE CARDINAL SIGNS

The three cardinal signs are the gross appearance of the urine, the edema, and the hypertension. Each is unique. Their conjunction is pathognomonic.

The best description of the urine at the beginning of a glomerular nephritis is not to be found in the textbooks. We get it from our patients. They say "The urine looked like coffee." The simile is precise. This is so much the case that when we are trying to reconstruct the past in those patients in whom the initial stage was not observed, this reference to coffee comes to have a rather decisive significance. This is because the description is not only apt and true but is uniquely true for the initial stage of glomerular nephritis. The hematurias that occur in essential hypertension, renal tumors, or tuberculosis of the kidney give a red, not a brown, urine. These are gross arterial hemorrhages in which fresh blood dominates the picture. But at the onset of glomerular nephritis there is much more than blood in the urine, and the blood

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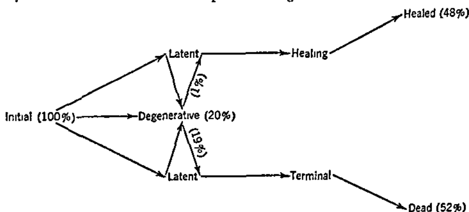


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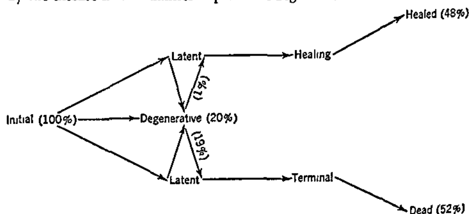


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Cast formation is a complicated process, markedly influenced by urine volume and urine reaction variation. The cell and protein excretion rates, on the other hand, are relatively uniform, and there is, in fact, a rather remarkable parallelism between the rate of protein and of epithelial cell excretion. This has some practical significance. In the past we have relied on counts of epithelial cell excretion as a guide in deciding when the protein in the diet could be increased or when the patient could be allowed to be up and around. We thought that the number of these cells might be taken as an index of the degree of impediment to the nutrition of the tubule cells. As the glomerular obstruction lessened we imagined the tubule cells getting more oxygen and food and supposed that this was the reason why there was such a regular decline in epithelial cell excretion. We still believe this is a substantially correct view. But Figure 43 shows us what we had not suspected, namely that the rate of protein excretion might have been used empirically as a guide with the same results. We now use both together and thus obtain a greater certainty.

DIFFICULTIES IN DIAGNOSIS

When all the three cardinal signs are present, they give us a quite unequivocal diagnosis. Then we do not need to wait for developments and can reach a decision at the first visit. This is true in spite of the fact that the renal, the capillary, and the cardiovascular manifestations differ in their absolute and relative intensities so that, in respect of the relations between these three groups of symptoms, each patient is unique. Difficulties in diagnosis arise in the exceptional patients in whom this always-present individuality becomes extreme, and one or another of the three cardinal signs becomes so prominent that we do not notice the others. When we first see these patients we may think that some of them have an acute pyelonephritis, others an anomalous generalized edema, while there are still others who quite obviously are suffering from a sudden cardiac failure, the reason for which we do not comprehend.

When the brunt of the disease falls on the kidney it may happen that there is no edema we can detect and, lacking any knowledge of the patient's usual blood pressure level, we may not be sure that there is any hypertension. When we look at the urine we may see only a great multitude of cells, that might well be pus cells, lying among even larger numbers of fragmented red blood-corpuscles. During the first few days, in these and in many other patients in the initial stage, the almost pathognomic mixed blood and epithelial cast may be absent or hard to find, and, if we restrict our attention to the sediment alone, it will seem that we have positive evidence of an acute urinary tract infection. The error

The most distinctive qualitative feature of the sediment is the mixed blood and epithelial cell cast. It constitutes the majority of the casts at the very beginning. It contains within itself all the story of what has happened in the nephron. There is needed for its formation an inflammation in the glomerulus sufficiently severe to provoke the exudation into Bowman's capsule of a bloody fibrinogen-containing fluid. There is also needed within the tubule lumen a fluid rich in dead tubule cells that have been suffocated by the obstruction in the glomerulus to the red cell flow that brings them oxygen. As the filtrate concentrates in the lower reaches of the tubule, the fibrinogen clots and entangles in its meshes the tubule cells and red blood-cells so richly present in the fluid. This cast thus incorporates the products of both glomerulitis and tubule cell death.

The initial stage sediment can be described quantitatively in terms of the rates of excretion of formed elements and of protein, but there is such a rapid decrease in the intensity of the lesion that the absolute figures have no significance unless we know the time, after the onset, at which the measurements were made. In Figure 43 we give the average measurements made on twenty cases in which we were able, in the midst of more practical work, to get a sufficient number of points to let us block out the rate of change in 5-day periods. Even in these cases the data are not in every instance continuous over the whole period, and the average curves we give are derived from a summation of smooth curves drawn through the actual observations in each patient.

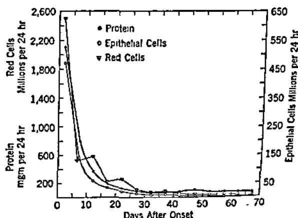


Fig. 43. Rates of excretion of protein, red cells, and epithelial cells from the onset of the initial stage.

In Figure 43 we have given only the rates of protein, epithelial cells, and red cells. There is a general decrease in the rates of cast excretion as time elapses from the onset, but the curves are quite irregular.

portion that died in uremia was 20%. The remaining 7% died of other disease not directly connected with their nephritis. If we exclude this last group and two patients who died of cardiac dilatation in the initial stage, we find that 80% recovered and 20% went on to die in the terminal stage. But the mortality in all patients who develop glomerular nephritis is almost certainly much less than 20%. Our group is not free from selection. We see particularly the patients in whom the initial stage is severe, and we are likely to be able to follow to the end especially those who die in uremia. The question might be decided if we could follow all the patients who develop glomerular nephritis in scarlet fever wards, though we may suspect that we should then come across a new difficulty through the discovery of initial stages so mild and transient that our diagnosis would be in doubt.[4]

DURATION OF GLOMERULAR NEPHRITIS IN PATIENTS WHOSE LESIONS HEAL

We used to think there was practically no chance of healing if evidences of a continuing lesion were still found two years after the onset (59). We are glad to be able to correct that too gloomy view. It was based on inadequate experience. As we continued to watch these patients we found that year by year a few would give us urines in which there were no blood-casts, no abnormal number of red cells, and no more than the normal quantity of casts and protein. These were patients in whom there were no extrarenal manifestations of disease, and we can

TABLE 36

TIME BETWEEN ONSET AND HEALING OF GLOMERULAR NEPHRITIS

YEARS	NUMBER	%
0 to 0.5	21	23.9
1.0	27	30.7
1.5	12	13.6
2.0	12	13.6
3.0	5	5.7
4.0	2	2.3
5.0	2	2.3
6.0	2	2.3
6 to 10.0	5	5.7

[4] There has been an interesting controversy in the pediatric literature as to the propor- [illegible] of glomerular nephritis through their observation of the curious color of the urine at the onset of the initial stage.

contradicts it, for the fact that there seems to be no close correlation between the severity of the renal lesion and the degree of edema or the height of the diastolic pressure is in no way decisive. It only makes it seem more likely that all three abnormalities are effects produced by some factor we have not yet isolated—perhaps the by-product of an antigen antibody reaction.

Such speculations go beyond the evidence we can derive from clinical observation. If we stay within the scope of what we ourselves see, the most that can be ventured as a connecting link between our observations is the suggestion that at the very beginning of glomerular nephritis there may be a sudden dilution of the plasma.[3] A rapid increase in total plasma volume would certainly help to explain some of our facts. There is, for instance, the mild anemia and the low serum protein concentration we see at the very beginning, and the fact that the systolic pressure is raised even more than we should expect from the diastolic level so that the hypertension of the initial stage is characterized by an increase in pulse-pressure and is often associated with a slow pulse rate. Most important of all, this hypothesis, if validated, would enable us to prevent as well as to treat the cardiac failure of the initial stage. Such problems as these cannot be solved in the out-patient department. They will be answered by systematic investigation in the ward.

NUMBER OF PATIENTS IN WHOM INITIAL STAGE IS OBSERVED WHO REACH THE TERMINAL STAGE AND DIE WITH RENAL FAILURE

If we consider all the patients with glomerular nephritis we have followed to the end, we find that 52% of them die of uremia in the terminal stage. That has very little meaning, except to us, because it refers only to the sort of patients who come to a special clinic for Bright's disease. It does not tell us how many of all the people who develop glomerular nephritis will finally succumb to the disease, because we see more of those who are on their way to death than of those who are on the road to recovery. We come closer to what we want if we exclude the patients who come to us in the latent, the degenerative, and the terminal stages of the disease, and all those who have not been seen in the initial stage or of whom we have no knowledge as to when the disease began. We have 118 patients either seen in the initial stage or seen so soon afterward that there is no doubt as to the time of onset. We watched 73% of this group as the evidences of a renal lesion slowly disappeared and until repeated examinations failed to show any abnormality. The pro-

[illegible] that an increase in blood
L. Cardozo, in a
[illegible]nd, 125 553, 1946.

on which to base a judgment as to when the initial stage began, as in the case of Mrs. S. and Mrs. B. for whom the essential facts are given in Tables 38, 39, and 40, or is one of those patients about whom we are sure because we have watched them from the very beginning of the disease, we come now to that long period in the development of glomerular nephritis in which it seems as though nothing were happening. Day by day, week by week, month by month, and year by year we see the same person, without any complaints, with a normal blood-pressure and cardiovascular system, but showing always in his urine the same evidence of a continuing renal lesion, and the same moderate decrease in the amount of effectively functioning renal tissue. This appearance of rest and harmony is an illusion. There is a great deal going on though we do not see it. It is such a quiet as supervenes when two opposing forces are evenly balanced and neither prevails. Immediately after the sudden onset of the disease the reparative forces are able to counterattack so strongly that we can see and measure the advance. Toward the end of the latent stage an increasingly rapid failure to hold the ground rewon becomes evident. But here, in this intermediate phase, there is victory or defeat for neither side.

We can get beyond the realm of metaphor by considering the measurements made in three of our patients with latent glomerular nephritis who are still under observation. We select them not because they are in any respect singular but because we have been able to watch them

TABLE 37

MR. H

YEAR	AMOUNT OF EFFECTIVELY FUNCTIONING RENAL TISSUE	RATES OF EXCRETION PER 24 HR URINE			
	% of normal (100%)	protein mgm	casts	red blood-cells, millions	white and epithelial cells, millions
1923	78	418	110,000	25	14
1926	65	604	66,000	33	12
1927	61	486	20,000	46	30
1930	72	225	6,800	4	7
1931	58	202	5,000	5	3
1932	54	388	45,000	4	1
1936	54	376	66,000	10	5
1939	63	420	66,000	4	4
1946	53	140	0	8	1

Mr. H. was [illegible]

In 1946 his blood-pressure was $\frac{[illegible]}{70}$.

these nephrons will increase, but something is irrevocably lost, for their total number is forever diminished.

Glomerular nephritis in the latent stage is not infrequently diagnosed at an indeterminate point of time since an unobserved onset. An example is Mr. H. about whom some information is given in Table 37. He may be taken as representing many of the patients we are still observing. As a rule the investigation that leads to this diagnosis is initiated by the observation that the urine contains a small amount of protein. The reason that the urine is examined at all is that these people want insurance or employment. They have no complaints and physical examination fails to reveal any significant abnormality. In this group the rate of protein excretion is usually somewhat higher than the average rate found in the group whose renal lesion healed within the first 2 yr after the onset (Figure 43). In that first group the usual routine examination for urine protein would not have indicated any noticeable albuminuria unless the urine had happened to be more concentrated than usual. In the urine of the patients we are now considering there is often enough protein to give a positive qualitative test for albumen in almost any specimen that may be examined. This suffices to raise the question of the nature of the renal lesion, but the differentiation of latent glomerular nephritis from all the other conditions that may lead to a slight proteinuria is not always easy. The association of the proteinuria with hematuria and cylindruria is not enough. There is a great multiplicity of situations in which that conjunction is found. But the constancy of the hematuria in latent glomerular nephritis is a rule that seems to be so free from exceptions that, from a negative point of view, we are inclined to rule out a diagnosis of latent glomerular nephritis if, in examining a series of urines, we find even one acid and concentrated specimen that contains no red blood-cells. No matter at what time of the day or night, or at what season of the year we examine the urine, and no matter how long the period over which we reiterate our search, every such specimen will reveal this continuing, microscopic hematuria. Certainty is reached when the typical latent stage blood-cast is found. That usually requires special methods for concentrating the sediment. There are often very few of these casts and they are hard to find if the urine contains much mucus. And, of course, the certainty is relative, not absolute, for precisely the same blood-casts and the same constancy of hematuria is found in the early stages of Streptococcus viridans septicemias in people who may not be very obviously ill.

Whether the patient with latent glomerular nephritis is, as in the case of Mr. H., someone in whom the duration of the nephritis is unknown, or belongs to the group in whom there is fairly good evidence

glomerulitis, acute in the pathological sense, since it involves the diapedesis of red cells and the passage of a fibrinogen containing exudate through the glomerular membrane. These observations have been made over considerable periods of time—for 23 yr in the case of Mr. H, for 15 yr in the case of Mrs. S, and for 19 yr in the case of Mrs. B. Surely, in, for instance, Mrs. B, the glomeruli through which we have good reason to believe red cells and fibrinogen were passing in 1914 are not the same glomeruli from which they are coming in 1946. In a structure as delicate as the glomerular tuft it is hard to believe that an acute inflammation could be so long endured. One would expect that in no great length of time the process would eventuate either in healing or in occlusion of the tuft, with death of the whole nephron, or, at best, the continuation of the tubule in an aglomerular form. It seems inevitable that we should suppose that over all these years there was a continuing loss of nephrons and see the lesion as, in this sense, progressive.

We have stressed the seemingly reasonable idea that glomerular inflammation must induce an unremitting loss of nephrons as long as it continues because we should anticipate that, even though the rate of loss were low, the accumulation of loss over periods of from 15 to 32 yr would be revealed by a decrease in the amount of effectively functioning renal tissue. This anticipation is not substantiated by the measurements. The tables show that in these three patients the amount of effective renal tissue has remained substantially constant.[5]

We are thus faced with what seems to be a contradiction between the inferences we draw from our two sets of measurements. From the urine we infer the existence of a pathological process that induces a cumulative and irrevocable decrease in nephron number, and from the measurements of the extent of the renal lesion we infer that over all these many years there has been no significant decrease in the amount of effective renal tissue. The logical solution is to accept both inferences as valid. We can admit that the number of nephrons must have been constantly diminishing and maintain that the amount of functioning renal tissue was held constant by a compensating increase in the size and efficiency of the nephrons that remained. We are predisposed toward the acceptance of this solution because it is in harmony with one of the principles that emerges from our experimental work and because it is supported by Oliver's measurements of the increase in the thickness and the length

[5] The first experimental demonstration of the principle involved in the method for measuring the amount of effectively functioning renal tissue used in these patients was given in 1916 (64). After we had developed its clinical application and had used it for many years we described it in 1922 (22). There was subsequent experimental evidence that in healthy animals the method yields results that vary directly as the amount of effectively functioning renal tissue (34, 35, 36).

TABLE 38

MRS. S.

YEAR	AMOUNT OF EFFECTIVELY FUNCTIONING RENAL TISSUE % of normal (100%)	RATES OF EXCRETION PER 24 HR URINE protein mgm	casts	red blood-cells, millions	white and epithelial cells, millions
1931	79	1,502	640,000	23	5
1933	82	590	280,000	388	4
1935	84	1,238	180,000	17	3
1938	73	2,320	500,000	12	16
1942	81	2,950	460,000	5	2
1946	74	889	0	4	2

In 1929, when she was 11 yr old, during the course of a severe pansinusitis, her mother saw that her face was swollen and that her urine had a cloudy brown or red color. Her doctor made a diagnosis of acute nephritis. When we saw her in 1931 it was only in the urine that we could find any abnormality. In 1944 she went through a normal pregnancy. In 1946 her blood-pressure was $\frac{120}{90}$.

TABLE 39

MRS B.

YEAR	AMOUNT OF EFFECTIVELY FUNCTIONING RENAL TISSUE % of normal (100%)	RATES OF EXCRETION PER 24 HR URINE protein mgm	casts	red blood-cells, millions	white and epithelial cells, millions
1929	73	260	800,000	20	10
1932	71	194			
1937	73	148	0	97	7
1939	62	200	200,000	50	4
1944	71	50	10,000	125	3
1946	70	180			

In 1914, when she was 15 yr old, after recovery from tonsillitis it was noted that her urine had a dark red color. Her doctor made a diagnosis of acute nephritis. We saw her first in 1927 when she was referred because the urine had become red with blood during the first day of a tonsillitis. She has remained in good health since that time. In 1946 her blood-pressure was $\frac{120}{80}$

over a considerable space of time. The data are given in Tables 37, 38, and 39.

Here are three patients who have had glomerular nephritis for a long time: In the case of Mrs. S for 17 yr, in Mrs B for 32 yr, and in Mr. H., though we do not know when it began, we are sure it has lasted for at least 27 yr. In these patients we have a consecutive series of measurements of the rates of excretion of protein, casts, and cells, very many more than we give in the tables. Always we have found a microscopic *hematuria, and on every occasion on which we* have made a special search we have found blood-casts. We infer the existence of an acute

The latent stage comes to its close in one of three ways: First, in 80% of patients we were able to watch from the start the rates of red cell and of protein excretion slowly fall, until blood-casts could no longer be found, and finally there was no abnormality of any sort to be discovered in the urine or in the patient. This is what we call the end by "healing." Second, in a small number of patients we have seen the latent pass into the degenerative stage. These are patients in whom the rate of protein excretion is, as a rule, higher than we ordinarily find in the latent stage, and the first indication we get of a change is an increase in protein excretion, from, let us say, 1 to 3 gm to a level of from 5 to 10 gm per 24 hr. Soon afterward the rate of tubule cell excretion begins to increase and we find casts of the epithelial variety, epithelial, granular, and waxy casts. Sooner or later there may be a gradual decline in the serum protein concentration, and then we may expect to see the first beginning of what will later be a generalized anasarca. This is not, however, an invariable sequence, and there are some patients with all the evidences in their urine of the existence of a degenerative renal lesion whose serum protein concentration never falls so low that they become edematous. Third, there may be a gradual transition from the latent into the terminal stage. It is this last mode of ending we shall discuss.

The factor that determines the transition from the latent to the terminal stage is a reduction in the amount of effectively functioning renal tissue. All of the clinical signs that now begin to appear—the dilute urine, the broad renal failure casts, the anemia, the hypertension, and the uremia—can be reproduced experimentally in animals by a reduction in nephron number. But that is only true under certain conditions. No doubt if we pushed the simple reduction in number to an extreme, that factor alone might suffice, but when three-quarters of the total number of nephrons are removed, these signs appear only when we increase the demand for osmotic work by giving food that contains more than the usual amount of protein. In this case the renal failure is not inevitable; it is a relative, not an absolute, failure. We believe that people with glomerular nephritis in whom a large proportion of nephrons have been destroyed are in much the same position as our rats that have only a quarter of their original number of nephrons left. Whether their kidneys are sufficient or insufficient depends on what their kidneys are required to do, and that, again, depends on what they eat and drink.

In practical clinical work the first sign of impending failure will often be a gradual rise of serum creatinine concentration. In the past we have been guided by the level of concentration of urea in the serum. That is an ambiguous index unless the patient is controlling his protein consumption within known and narrow limits. Most of our patients

of the proximal convoluted tubules when the number of nephrons is decreased (Figure 9).

Nevertheless we confess we are doubtful as to whether this view can be accepted as a complete account of what happened in these three patients. It is not that we doubt the general principle of an inverse relation between the number and the size and capacity of the nephrons or that we are not confident that this solution will be found to be an important element in a full explanation of the clinical facts. Our doubt and hesitation arises because, although our requirements are met, we cannot expect others to be equally satisfied. What would a pathologist think about an acute glomerulitis that, we tell him, has continued over 32 yr and that nevertheless, for the last 17 yr, has left the patient with about 70% of the amount of renal tissue to be expected for her size and weight? If he were willing even to entertain the idea it would seem that he would be obliged to conceive it as a focal lesion, present at any one time in only a few of the glomeruli but spreading from one to another, so that as one glomerulus and its tubule succumbed and was reduced to fibrous tissue, another would become acutely inflamed. But this idea of a spread from one glomerulus to another is one for which there is no evidence at all. It is, in fact, no more than an *ad hoc* hypothesis.

We are therefore inclined to question our assumption that the blood-casts we see in the latent stage necessarily indicate an acute inflammatory process of the ordinary type in the glomeruli of the nephrons from which they came. In the initial stage this is an assumption supported by the direct observations of pathologists, but what do we know about the structural changes in the glomeruli of patients with latent glomerular nephritis? Certainly we have no knowledge that the inflammatory reaction in the glomeruli in the latent stage is similar to the reaction in the initial stage, the only difference being that in the latent stage only a few instead of all the glomeruli are involved. For all we know the blood-casts we find in the latent stage may not be the products of an "ordinary" acute inflammation. Perhaps this latent stage glomerulitis endures as an X-ray burn endures, manifesting over decades many of the signs of an acute inflammation but never coming to a decision toward either life or death. Perhaps in the initial stage the lesion involved the chromosomes of the endothelial and epithelial cells of the glomeruli, and these crippled cells, with permeability characteristics that allow the passage of fibrinogen and red cells, go on reproducing their kind, for generation after generation, through long stretches of time.[6]

[6] Uranium, given to animals in one injection of one or another of its salts, may be followed by a long-continued and progressive renal lesion. This is not true for injections of mercury, chromium, or lead salts

undiagnosed cases of glomerular nephritis is to invite immediate correction. It is certainly not generally true of children under 5 yr of age, and it is not absolutely true of all adult patients with this syndrome. In every few hundred patients there may be several who do not have glomerular nephritis and yet have all these symptoms. If, then, we are wholly absolute in our views on this question, we will fall into error in diagnosis in a small percentage of all cases. We may grant this and still insist it is better to be right in 99% than doubtful and frustrated with respect to action in 100%. Error is only to be feared if it damages the patient. In this instance error will hurt only our quite unreasonable desire to be infallible. A diagnosis is not like the solution to an equation. It is always incomplete, and the more concrete and specific it becomes, the more certainly will it include error as well as truth. It is nothing in itself. Unless it leads to effective action it remains a merely verbal and academic exercise of the intelligence—a sort of Jack Horner's plum we extract for our own vainglory. The diagnosis of nephrosis leads to a purely symptomatic treatment of the edema The long odds are always against it. The patient will be harmed if we are wrong. Therefore we maintain that all patients with this syndrome should be treated as though they were in the degenerative stage of a glomerular nephritis.

We have described what appears to us to be the obvious clinical facts observable in most patients who first come under observation because of edema.[1] In our series, some had been seen by our colleagues in the initial stage or gave such a clear history of it that there was no reasonable doubt as to the diagnosis. There were other patients, already under observation in the latent stage, in whom all these symptoms developed after some severe and rather prolonged infection. There is yet another group, not so uncommon in out-patient practice, some of whom may give a clear history of the initial stage, in whom the intensity of the renal lesion seems never to have fallen to the low levels usually found in the latent stage. In the clinical sense they are latent, without any abnormality of the blood and with blood-pressures well within the normal range, and it is only their relatively high rates of protein, cell, and cast excretion that make them singular. In such patients we may see a gradual transition to a fully developed degenerative phase, but without the interposition of the prolonged and severe infection which seemed to be the predisposing cause in the second group. These three groups nearly ex-

[1] There are those who stress other abnormalities, for instance a lowering of metabolic rate. Our experience does not show that this is a necessary part of the clinical picture If a patient takes about 40 gm of protein a day, and loses 30 gm every day in the urine, it will not be long before he shows all the effects of protein starvation A lowering of the basal metabolic rate is one of these symptoms

fatty infiltration in glomerular nephritis is not diffuse. In sections we see it only here and there, because it involves merely a part of the whole tubule. In the sediment, too, most of the epithelial cells do not contain fat. In this stage there are sometimes very few red cells, perhaps only 1,000,000 or 2,000,000, though in most cases there are still 5,000,000 to 50,000,000 pale red cells among the casts and fat droplets and epithelial cells. Lastly, when we take 5 cc of the supernatent fluid and add the phosphotungstic acid, we get a thick, white precipitate that is packed into a volume of 2 cc after centrifuging. The sample we have taken is only 1 part in 120 of the 24-hr volume so we can visualize the mass of protein excreted in 24 hr as filling a volume of 240 cc. This means the patient is losing about 15 gm of protein in his urine every day.

We have repeated a description of the salient abnormalities seen in the degenerative stage because it is important to have it clearly before us when we consider what is to be done; important, because it is difficult for doctors and almost impossible for patients to see what is behind the edema. Edema is an abnormality so obvious and striking that it is apt to become in itself a diagnosis. We should then tacitly suppose that the cylindruria, the fatty infiltration of the tubule cells, the lipemia, and the proteinuria came with the edema, and we shall regard them as subsidiary manifestations of the "nephrotic" syndrome. Clinicians of great experience have, in fact, adopted this view. They suppose that a patient such as we describe is the victim of a disease *sui generis*, and they call this supposed entity "nephrosis." No one can deny that they have some justification. But "nephrosis" is really not a diagnosis in the full sense of the word. It only gives a name to symptoms that appear suddenly from nowhere, without any history of development. "Nephrosis" is at best a nominal interim diagnosis, a convenience for the moment, not a term that reminds one of any story that has a beginning and an end. No one will ever know the beginning of the condition in most of those patients, but the beginning was there and was dramatic enough though no one noticed it. It was the initial stage of glomerular nephritis. If we wait long enough we shall see the end. It will be the end to which all patients with nephritis come who do not heal or die of intercurrent disease before the final uremia. What is important is not that the diagnosis of nephrosis is usually shown to be incorrect; what matters is that this so-called diagnosis may harm the patient. This is more than a quarrel about words, for when we say a patient has nephrosis we, in effect, decide that the edema is his central ill and that we should use the most energetic measures to rid him of it, including some that we think are risky if the patient really has a glomerular nephritis.

To say that all instances of nephrosis are nothing more or less than

increase in the permeability of the glomerular membrane. There is no increase in red cell or blood-cast excretion from which we might infer an exacerbation of the process of inflammation in the glomeruli. The single change we see is that there is more protein in the urine than before. Therefore, in the light of what has been found about protein reabsorption by the tubule cells, we conclude that the increase in protein excretion arises because less of the protein that comes from the glomeruli is being reabsorbed, and we attribute this to a failure of the tubule cells. This conclusion is simultaneously or very soon afterward confirmed by the appearance in the urinary sediment of cells swollen with granules that we suppose are cells like those cells full of hyaline droplets that Oliver finds, except that the cells we see have died because they have become so glutted with reabsorbed protein.

But granted that the increased proteinuria is a consequence of a failure in protein reabsorption by the tubule cells, the question still remains as to why some patients who for considerable periods of time have succeeded in reabsorbing all but 1 or 2 gm of protein a day should now excrete from 5 to 20 gm a day. In most of the few patients in whom we have some evidence as to the mode of transition, there was an external reason in the form of an infection such as might have induced cloudy swelling and have led to interference with the process of protein reabsorption. But we have seen some patients in whom no such outside reason for the event can be assigned. It is such cases that suggest that there may be a limit to the process of reabsorption if we think of it as involving not only something corresponding to the phagocytosis of protein from the filtrate but as involving also the intracellular digestion of the protein that is reabsorbed. Our protein determinations in the urine give us no index at all of the quantity of protein that passes the glomeruli. A patient in the latent stage who excretes only 1 gm of protein a day may very well have to reabsorb every day many times the 30 or 40 gm we have reason to suppose the normal kidney recovers. If there is a limit to this process it would be in a disease in which there are anatomical reasons for an increase in the quantity of protein passing through the glomerular membrane that we might expect to see this limit sometimes exceeded.

With the advent of the next clinical sign in the development of the degenerative stage we lose contact with physiology and pathology and our clinical facts become no longer comprehensible. What we do not understand is the gradual fall in the concentration of protein in the plasma until, in many instances, the patient becomes grossly edematous It is just at this point that we have to stick to the kidney where the only disease we have been able to detect exists. If we have to resort to hypothe-

of plasma proteins; but in glomerular nephritis, after the initial stage has passed, the renal lesion is central. It is within the kidney that we must look for the origin of the sequence of events that we observe, because if we once allow ourselves to postulate primary extrarenal factors, for which we have no evidence whatsoever, there will be no limit to the multiplication of hypotheses. If we accept this restriction, and remember how, in the transition from the latent to the degenerative stage, the first and for a time the only change we can detect is a substantial increase in protein excretion, it is reasonable to ask whether this degeneration may not have its origin in some defect in the mechanism of protein excretion.

In Chapter 2 we quoted the recent demonstration that the glomerular filtrate of mammals contains some protein. We pointed out that if we assume this to be true in man and take the conservative estimate of a protein concentration in the filtrate as low as 20 mgm per 100 cc, then, knowing that the filtrate volume is about 180,000 cc, the protein filtered every 24 hr will be about 36 gm. Thus we may suppose that about one-fifth of the total amount of plasma protein in the blood daily leaves the circulation and enters the renal tubules. But this 36 gm does not leave the kidney through the urine. All but a few milligrams are reabsorbed. The process of reabsorption has been proved by Oliver. When we injected dyed proteins into our rats he demonstrated the accumulation of the dyed protein inside the cells of the proximal tubule (65) and thus confirmed, in a concrete way, a great deal of evidence of various sorts that all combines toward the conclusion that reabsorption of protein from the glomerular filtrate is a function of the normal kidney.

The reabsorbed protein does not remain as an accumulation within the cells. In a short time it disappears. How? Not, one would suppose, by a simple diffusion or transport of unaltered protein molecules out of the cell into the tissue spaces and into the interior of the capillaries and lymphatics. We can believe that unaltered proteins are taken into the cells from the filtrate within the lumen of the tubule, because we find them reabsorbing substances like fats that have a considerable molecular volume, and we can think of the entrance of protein molecules into the cell from the glomerular filtrate in terms of a modification of the process we call phagocytosis. But the exit from the cell of the gross particulate accumulations that Oliver finds is an altogether different matter. It is a more reasonable supposition that these accumulations are material that has to undergo intracellular digestion before it can leave the cell.

Let us return now to the observation that the first indication of the onset of the degenerative stage is a considerable increase in protein excretion. We can find no clinical evidence that this increase is due to an

absorption from the gastrointestinal tract. When pathologists make their examinations they find fat in the serum and in the kidney but no fatty infiltration or degeneration or abnormal accumulation of fat anywhere else in the body. But the protein chemists have ideas from which a reasonable explanation may be derived. When ammonium sulphate or potassium citrate is added in increasing quantities to samples of normal serum, the euglobulin precipitates out first, and as larger amounts are added to the tubes there is one that contains a precipitate that has a color and texture slightly different from any of the others. When this sample is denatured and extracted with fat solvents, it is found to contain a much higher proportion of fat than any of the other precipitates. In the Tiselius this protein moves with the first part of the beta fraction. It is the protein that "carries" the fat but carries it hidden, so that we do not see it and cannot even get it out with fat solvents until the protein is denatured. The first stage of denaturation involves the unfolding of the two long layers of linked amino-acids that, when they lie together, make up the structure of undenatured proteins in the plasma. It has been suggested that this particular protein that carries fat has the amino-acids of its two chains so orientated that the R—CH_2 groups are pointing toward the inside. This protein would then be like a long loop and a fatty acid molecule could creep inside the loop but would be repelled from the outside toward which the hydrophilic R—COOH and R—$CH(NH_2)$ groups are pointing A fat solvent could not get inside until the loop had been bent open In some such manner we can make a picture of how fat can be carried by protein molecules, and we can extend the image and see the milky plasma as the result of an absence of the plasma protein molecules that have this transport function. Then the fatty acid molecules from the gastrointestinal tract would be left free in the water of the plasma and they would coalesce into the little fat globules that make the creamy emulsion we see. There is, of course, more here than a simple change in the location of fat in the plasma; there is a considerable increase in fat concentration, but this is comprehensible as a consequence of something analogous to the traffic jam that occurs on the streets when our rapid transport systems fail.

The degenerative stage may end by a reversion to the latent stage or it may go on into the terminal stage. As a rule the transition to the terminal stage is so gradual that the patients do not notice that they are slowly growing weaker and more anemic, and they are only glad that the edema—the only sign that ever came to their consciousness—has finally gone. But there is a small group in whom the diastolic pressure rises to very high levels, and then we see conjoined in one patient the signs and symptoms of two diseases—the fusion of malignant hypertension and of

of the truth. What is asked of a hypothesis is not that it should precisely prefigure the mechanism that actually exists. All we require is that it should suggest questions that can be answered by experiment, and that it should emerge in the simplest possible manner and without contradiction from what we do know about the problem.

There are three clinical results that follow the decrease in plasma protein concentration, and that we suppose we can comprehend in terms of a diminution of one or another of these proteins.

The first is the liability of these patients to contract sudden and rapidly extending infections with streptococcal, staphylococcal, and pneumococcal organisms. In some of these patients Dr. Jameson has demonstrated an extreme reduction in gamma globulin. Of late several have been saved by penicillin. For some time we have given minute doses of sulfathiazole (100 mgm four times a day) to some of our edematous children who have had reiterated infections, hoping that it might have some prophylactic effect. We think that at the very onset of every fever penicillin should be injected.

The second is the quite frequent occurrence of venous thromboses. For some curious reason this has not, so far as we know, been described. In any part of the body, but most commonly in a leg, there is a sudden increase in edema, with pain, tenderness, and often a reddening of the skin. This is followed by a slight fever, a mild leukocytosis, and an increase in the sedimentation rate. Within 3 or 4 days the local swelling and tenderness subside. When this occurs in an arm it is sometimes possible to palpate the thrombosed vein. As Rytand suggests, this thrombosis may be a consequence of a decrease in circulating antithrombin which is one of the serum-albumins.

Lipemia is the third phenomenon of the degenerative stage that may be regarded as a consequence of the decrease in the concentration of certain plasma proteins. We can suppose we understand the presence of fat in the urine. We see the tubule cells choked with fat droplets as well as with protein granules. We can see these cells as they burst and liberate their contents into the urine. We see the same cells in their place in the proximal tubule when a patient in the degenerative stage happens to die. We can connect these minute fat globules with the lipemia and suppose that they came from the fatty blood, were squeezed through the glomerular membrane, and that most of them were phagocytosed from the filtrate by the tubule cells. But the creamlike plasma we see when we centrifuge the blood of these patients is not immediately comprehensible. It is not a consequence of a general dyscrasia of fat metabolism. In these patients Van Slyke and his coworkers (67) found no defect in the anabolism or catabolism of fat and no anomaly in fat

in hospitals, and it is those who have there made detailed investigations of patients in uremia who are most competent to describe the objective aspects of the very end of the disease What is learned in the out-patient department is conservatism in prognosis and the importance of not letting the patient become aware of our fears as to his fate. We see many patients who are uremic, perhaps even deeply uremic when they first come to us, who yet improve and live and work in comfort for a long time. This is due in part to dietetic treatment, but usually it is due to the circumstance that an accidental and remediable dehydration has led to a transient intensification of their uremia and thus for the first time brought to their consciousness signs of a state that has long been with them. It is in following patients with latent glomerular nephritis as they pass into the terminal stage that the long duration of the preuremic and uremic phases of the disease is best appreciated, and that the need for care in prognosis becomes most apparent. These are patients we have known for a long time; they are those as to whose ultimate fate we can be as sure as we can of anything in clinical medicine. Year by year we have watched their blood urea concentrations rising, their urine becoming more dilute, and their anemia deepening, and this in spite of all their dietetic endeavors. When the doctor sees them, it is with a fear that someday they may ask him explicitly what is the precise meaning of these measurements that are being made. Do the results show that they are getting better? But he need not be afraid. They never ask the fatal question. It may be that, implicitly, they already know the answer—know it in a much more profound sense than the doctor. If so, they are undismayed and cheerfully carry on, much as all of us carry on though we know that someday we shall die. We do them an ill service if we force them to participate in our fears or even in our certainties. They do not listen to us. They wait for deeper intimations of their mortality. That voice they will hear because it is their own, and that message they will receive with no resentment or dismay.

irregularly but over the years quite unquestionably, by a gradually deepening anemia, by a creatinine or blood urea concentration that increases, on the whole, with a steady persistence, and by certain urinary changes that in the end become unmistakable.

For patients in the degenerative stage the road to the terminal stage is not, as a rule, so long. By what, on a superficial view, seems a cruel paradox, the transition presents itself to them as a release and a deliverance from the only symptom that has troubled them—their edema. Ultimately both those who came from the latent stage and those who used to be in the degenerative stage come, at the end of their course, to be as *much alike as they were at its beginning. The distinguishing characteristics* of the degenerative stage—its edema, lipemia, exaggerated proteinuria, and the evidence of a fatty infiltration of the tubule cells—*gradually fade away, and both those who were degenerative and those* who were latent come to have much the same uremia, hypertension, and anemia, and all alike excrete a urine that is always dilute, that contains more protein than in the latent but less than in the degenerative stage, and one in which a qualitative sediment examination will often reveal a few broad renal failure casts.

There is now a greater constancy than ever before; a constancy dictated by the small number of overworked nephrons still functioning. It is because the nephrons are few and overburdened that the urine is so dilute and yet contains so much protein. It is because they are few that in spite of the fact that they cannot recapture the usual proportion of the water of the filtrate, their total contribution of urine to certain tributaries of the collecting tubule system is only a trickle of urine that allows *the cells and cell detritus to clump together into these big casts.* The whole urinary picture is now dominated by the reduction in nephron number, and little remains to remind us of the initial lesion that was once so unmistakable and unique—very little that gives us any inkling as to the long and often winding road that has led to this end. If we have not come down the road with the patient, if we have not already mapped its main contours, we cannot reconstruct it from what *is now* given. There are many roads that converge toward termination in an altogether insufficient number of still-functioning nephrons, and the end of all of them is as uniform as their origins are diverse.

We will not give any *detailed description of the various forms* under which the terminal stage makes its appearance nor any statistical presentation of its symptomatology, since such data have been adequately presented by those who have had much more opportunity than we to explore the interesting metabolic anomalies that sometimes occur as a result of renal failure. This is particularly the field of those who work

larger than he is and six hundred times larger than his kidneys. And once we have an answer to this question, we have the answer to another—the one with which we are now directly concerned: "What is the amount of fluid that the kidney moves from the tubules into the blood against osmotic pressure?" We know that the volume of urine excreted every 24 hr amounts to about 2,000 cc, so almost all of the 180,000 cc filtered is transferred from the tubules to the blood and the mass moved every 24 hr is 178,000 cc.

Work of the Kidney as Formulated by Physical Chemists

The movement of this very considerable mass is accomplished by overcoming the force of osmotic pressure. Left to itself the water would not go back to the blood, and the urine would remain an unconcentrated filtrate of the plasma. We have to look for some source of energy to move this mass of material, and we can find it only in the tubule cells. These cells must be capable of producing the energy needed for this external work in the same sense that muscle cells produce the energy needed to move masses of material against the resistance presented by the force of gravity. Now, given a mass, a resisting force, and a source of energy, physical chemists have derived equations that formulate the quantitative relations existing between the factors involved in different sorts of work. They have considered the problem of work when it is done against the force of osmotic pressure, and their conclusion, presented in a form that can be applied to such a concentrating mechanism as the kidney, is given in the following formula:

$$\text{Work per 24 hrs} = (NRT) \times \left(2.3 \log\frac{U}{B} - \frac{U-B}{U}\right)$$

in which

N = weight in mols of an excreted substance,
R = the gas constant (1.987 calories per degree),
T = the absolute temperature (37° C + 273° C = 310° C),
U = the concentration of the substance in the urine,
B = the concentration of the substance in the blood plasma,
2 3 = factor to convert common logs to natural logs.

The N for any substance is its 24-hr rate of excretion in grams divided by its molecular or ionic weight in grams. This mode of expression is used because osmotic effect depends on the number of molecules or ions dissolved in the water of the urine.

$\frac{U}{B}$, the concentration ratio or the number of times by which the concentration of a substance in the urine exceeds its concentration in the blood-plasma, is unaffected by the unit in which the concentrations are

"What is the work of the kidney?" Work is a complex term that involves two factors: first, a certain material mass, and second, the movement of this mass against a resisting force. We do work when we lift a book from the table because a mass, represented by the weight of the book, is moved against a resisting force—in this case the force of gravity. The heart works because a mass of fluid, the blood, is moved against a force—in this case the resistance to distension offered by the walls of the arterioles. So also does the kidney work. It moves a mass against a resisting force. The mass moved is water from the glomerular filtrate, and it is moved from the interior of the tubules into the capillaries that lie outside the tubules. The resisting force is the force of osmotic pressure that arises when, as the water is moved out, the fluid left within the lumen of the tubules comes to contain a greater concentration of certain molecules than exists in the plasma within the capillaries. ✓

VOLUME OF GLOMERULAR FILTRATE

The question then comes up: "What is the total mass or volume of fluid filtered by the glomeruli over any given period of time?" This was the question that Rehberg (68) raised but it was Homer Smith and his collaborators, who, after much trial and error, have ingeniously answered this question (21). They found a starch called inulin that happens to have molecules of such a shape and size that they filter easily from the capillaries of the tuft through the glomerular membrane and, once within the tubule, do not leave it by passing into the tubule cells and also do not enter it through any other door than that provided by the glomerulus. When they determined the concentration of inulin in the plasma they were thus, in effect, determining the concentration of inulin in the filtrate in Bowman's capsule, for there is no measurable difference between the plasma and filtrate concentrations. And when, maintaining the concentration of inulin in the plasma by constant intravenous injection, they collected urine and determined the amount excreted over a given period of time, they were, in effect, determining the amount of insulin that had filtered through the glomerulus in that space of time. Thus, knowing the rate at which inulin was filtered and knowing the concentration in the filtrate, the volume filtered in that chosen time could be ascertained by dividing the rate of inulin excretion by the concentration of inulin in the plasma.

In this way they got a surprising answer to their question: "What is the volume of fluid filtered from the plasma by the glomeruli over any space of time?" When we think of it in terms of 24-hr periods, the time interval most commonly used in medicine, we find that kidneys of an ordinary-sized man filter 180,000 cc every day—a mass nearly three times

end result. In man, over a 24-hr period, approximately 180,000 cc of fluid has been transferred from the lumen of the tubules to the blood in spite of the fact that the final concentration of urea in the urine has been increased until it may be 100 times greater in the urine than in the blood. The formula tells us that this cannot be done without work and that the least amount of work required in the excretion of any substance will vary as the rate of excretion multiplied by a factor whose value depends on the number of times by which the concentration in the urine is greater than that in the blood.

Measurements of Urea, Chloride, and Creatinine Work in Man

The formula, taken as a whole, does not state that an increase in protein consumption, and thus in urea excretion, would necessarily increase the work of the kidney. It is conceivable that, as the rate of urea excretion rose, the urine urea concentration might fall, and the blood urea concentration might increase to such a degree that a diminution in the value of the second factor of the formula might cancel the effect of an increase in the first. Partly on this account but mainly because it is important to know how much the work of the kidney in normal individuals is influenced by the protein content of the diet, we asked ten residents and interns to take diets in which the protein content was first 0 5, then 1 5, and finally 2.5 per kilogram of body weight. They started each diet on a Monday and continued until the following Saturday morning. There was no restriction of water consumption. On Thursday and Friday 24-hr collections of urine were obtained in bottles containing sulphuric acid, and on both of those days samples of blood were taken before lunch between 11:30 A.M. and 12:30 P.M. We thus obtained sixty urine collections and sixty specimens of blood, divided into three groups of twenty each, corresponding to the three levels of protein consumption. Urea in both urine and plasma was determined by a urease aeration method that yields results of a fairly high degree of precision. Chloride was obtained by a modified Volhard titration method, and creatinine in both urine and plasma was estimated by the Folin and Wu method using an Evelyn colorimeter. A few of the urine collections were discarded because the creatinine rates of excretion suggested that not quite all of the urine had been obtained. In calculating the work for chloride excretion the chloride was expressed as sodium chloride, ionization was disregarded, and the concentration of sodium chloride in the plasma was assumed to be 540 mgm per 100 cc—all three unwarranted assumptions or procedures but involving errors immaterial in relation to our purpose. We wished only to determine the relative importance of urea, creatinine, and sodium chloride for the work of the

ing no more protein to our patients than they require, and we can decrease the value of $\left(2.3 \log \frac{U}{B} - \frac{U - B}{U}\right)$ by giving them enough water to keep their urine urea concentration low.

The formula says nothing about the mechanism through which a urine that is concentrated with respect to urea is produced, but when we try to think in concrete terms of how work may be done against osmotic pressure, it is helpful to hypothecate a mechanism. We imagine, for instance, a membrane through which water but not urea may be pressed. We suppose it is clamped across the lumen of a cylinder that contains water on one side of the membrane and a urea solution on the other side. We can understand that under these circumstances we could concentrate the urea solution if we exerted pressure on it with a piston, and can believe that we might have to push harder as the concentration of urea in the cylinder rose. This is the sort of work we can easily comprehend. But that is only one of the many ways in which the work could be done, and it is not the way used by the kidney. The tubule is not a passive membrane; it is a cylinder made of cells that are generators of energy derived from chemical transformations, or, as we usually put it, this is a living, not a dead, membrane. In the proximal tubule chemical laws overrule the laws of physics.

In the kidney it is the membrane that does the concentrating, not some force external to the membrane. Precisely how it works we do not know, but we are no longer entirely ignorant of certain general aspects of its mode of action Walker, Bott, Oliver, and McDowell (71) have recently published the results obtained in their difficult and ingenious experiments. They collected fluid from the tubules of rats and guinea pigs, marked the sites of puncture, and, separating out these nephrons from all the rest, were able to measure the distance from the glomeruli to the places where the tubules had been tapped. They found that all the way down the proximal tubule and as far as the distal tubule the total osmotic pressure was approximately the same as that in the plasma. That means that the total number of dissolved molecules was about the same per unit volume of tubule fluid and plasma. But the sorts of molecules in the tubule fluid were different from those in the plasma. By specially devised and extremely micro methods, they were able to show that the chloride, creatinine, glucose, and protein concentrations were dissimilar. They found higher concentrations of creatinine in the tubule fluid than in the plasma. This was also true for glucose when they administered phoridzin. These higher concentrations can only have been obtained by work, no matter what the mechanism by which they were obtained. The mechanism used, we do not know; we know only the

of a man who takes 2.5 gm of protein per kilogram of body weight as it would use when separating the urine of a man consuming 0.5 gm of protein per kilogram. But the kidney is an actual, not an ideal, machine, and it is important for clinical purposes to know how much energy is lost in the process of urine formation—how much energy is used, not in the accomplishment of work, but in processes that we may think of as analogous to "friction." When the kidney works, it gets its energy from the burning of fuel within the tubule cells, and so the total cost of work can be measured in terms of the extra oxygen needed. Barcroft (72) showed that the kidney excreting much urea used more oxygen than the kidney excreting little,[3] but the data from which we can get some idea of the "friction" factor in the kidney were collected by Dock (73). He measured the oxygen used by the kidney at low and high levels of urea excretion, as well as the rate of excretion of urea, and the concentrations of urea in the urine and serum. He was thus able to compare the minimum energy required for the added work, as calculated from the physical chemist's formula, with the actual increase in energy expenditure that accompanied the work. The energy lost in processes that we may regard as analogous to friction was four times greater than the energy that eventuated as accomplished work. Although we cannot conclude from these observations, made under very special conditions, that the kidney always uses as much or as little as four times more energy for work than is ideally necessary, we have at least a rough idea as to the magnitude of the "friction" factor, and we may be sure that the results of calculations from urine and blood data give only a fraction of the total amount of energy expended by the kidney in the preparation of the urine.

Effect of Change in Protein Consumption on the Size of the Kidney

We can now consider the work of the kidney from an entirely different point of view, one in which the mode of observation is more in consonance with our ordinary clinical procedures. When the work of muscles is increased, the muscle fibers increase in size. When the arterioles of the systemic circulation are long constricted and the force that the heart has to overcome in moving the blood is thus augmented, we observe that the wall of the left ventricle grows thicker and that its muscle cells become hypertrophied. We call this process "work hypertrophy." Now, although we know that the kidney works, we do not

[3] Repeatedly, this observation has been both confirmed and denied. We suppose that the disagreement may be a consequence of the fact that the increment of oxygen consumption due to increased osmotic work is such a small part of the total oxygen consumption of the kidney that it is difficult to measure. (See page 238.)

he would reply that the simplicity or complexity of the mechanism by which *the concentration is produced has nothing to do with* the question, and he would maintain that what he says is true even for a machine as complicated as the kidney. He would say that his formula holds for all concentrations that ever have been or ever will be attained, and he would be confident in his generalization just because he has eliminated all reference to the nature of the machine from his statement. If he concentrates a solution by pushing on a piston, thus forcing out water through a membrane impermeable to some substance dissolved in it, he *does not deny that he will have to work harder if there is friction,* but his formula does not take such variables into account. Nevertheless, in all real machines there exists some degree of friction, and so the statement in which the physical chemist has such confidence is idealized and abstract. If the formula were not abstract it could embody no general scientific truth. It is only because it is not true for any machine that it can be true for all machines. For the truth remains, though it is not a precisely accurate description in any concrete instance. No matter what the simplicity or complexity of the process of concentration, no matter how little or how much is lost in friction, a certain minimum of work is necessary to effect any given degree of concentration, and this minimum *can be determined with precision. Actually, more work will be necessary,* depending on individual variables that cannot be generalized, but of this least possible amount of work we can be sure.

The doctor, face to face with the particular patient who has come to him for help, will at that moment be impatient of considerations as remote as those we have been discussing. They cannot give him sure and direct help with the individual. For perhaps in this patient the "friction" that is neglected in the scientist's statement may be the all-important element that determines the amount of work required of his kidneys. Perhaps the machine needs oil rather than any decrease in the load of work. At that moment the clinician demands more than a knowledge *pertaining to all machines and to all time. He* needs information about this machine at this time, for now he is called upon to "speak as one that has authority, and not as the scribes."

Certainly abstract considerations, when introduced *into a clinical* discussion, can be justified only if their relation to the subject is clear and direct. It is true that we know that the kidney works. We know that we can vary the amount of work it has to do by changing the amount of protein eaten. But all we know is the least amount of work that an ideal, frictionless machine would have to do if, in any way whatsoever, it were to separate urine from blood. We know that the ideal machine would use more than four times as much energy in separating the urine

not due to an increase in the synthetic chemical work of the kidney? The answer to this is not that the objection is wholly wrong but that all the extra-osmotic effects taken together can account for only a part of the increase. When urea excretion is increased by incorporating urea in the food (and urea is a substance that enters into none of the chemical reactions of the body), we still get a marked increase in the size of the kidney, though it is not so great as when a similar increase in urea excretion is induced by the administration of protein (24).

SIMILARITY OF RATE OF GROWTH OF THE KIDNEY AFTER INCREASE IN PROTEIN CONSUMPTION AND AFTER UNILATERAL NEPHRECTOMY

There is another, and in some respects a simpler, way to observe the effect of an increase in osmotic work on the size of the kidney. When we remove one kidney, the remaining kidney is called on to do twice as

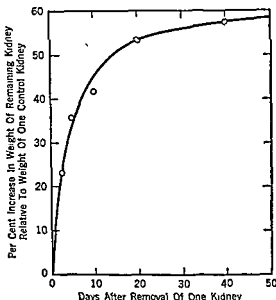


Fig 51. Effect on the weight of a kidney of the removal of the opposite kidney.

much work if the same diet is given and the same amount of protein consumed. The results of this operation are shown in Figure 51.

It is not alone the very considerable increase in the size of the kidney when the demand for its work is thus doubled that seems to us important in this result.[4] More convincing is the practical identity of the curves

[4] We must, of course, distinguish between a doubling of the demand for work at the moment when half the total renal tissue is removed and a doubling of the work actually accomplished When we measure the minimal amount of work done during the 24 hr

17% Protein | 0% Protein | 74% Protein

Kidney Weight mgm

1,800
1,400
1,000
600
200
0

0 10 20 30

Time In Days

Fig. 49

17% Protein | 74% Protein | 0% Protein

Kidney Weight mgm

1,800
1,400
1,000
600
200
0

0 10 20 30

Time In Days

Fig 50

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SIMILARITY OF RATE OF GROWTH OF THE KIDNEY
PROTEIN CONSUMPTION AND AFTER UNILATERAL

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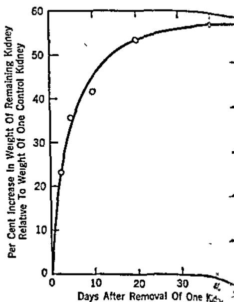


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[4] We must, of course, distinguish between a doubling of
moment when half the total renal tissue is removed and a
accomplished When we measure the minimal amount of

are in operation. Nevertheless, under any one set of relatively constant conditions all the changes that occur can be predicted and accounted for, at least approximately, on the basis of the amount of work the remaining kidney is required to perform per unit of functioning mass.

In themselves the data we have to present are far from satisfactory from the point of view of elegance and precision. In some degree this is a necessary failing—a consequence of the fact that the work of the kidney, *except in starved or sugar-fed rats, varies primarily with the* amount of food and water the animal takes. We felt that to control this variable factor would in all likelihood end only in the introduction of hidden variables affecting the blood flow through the kidney. Rats cannot be subjected to long-continued stomach-tube feeding without incurring this risk. It seemed to us better to use a lot of rats that were left free and undisturbed. This is a laborious way of removing a variable, and at certain points in our series of observations it seems likely that the number of rats used was inadequate, a circumstance that lessens precision. We intended to make our observation on the structural and functional changes induced by the removal of varying proportions of renal tissue at a time when all change had come to an end, and we allowed a period of 40 days to elapse after the operation. When the experiments were planned we were not aware that when 75% of the kidney *is removed the remaining fragment goes on growing for at* least 80 days (page 66). The time relations are thus defective for the data on the 75% removals. We have started another series of similar observations which we hope may, in another way, make up for these defects, though they are primarily intended to answer another question. It has also to be acknowledged that, since our method of collecting urine on blotting paper precluded the measurement of 24 hr urine volumes, we were obliged to depend for our estimates of urine urea concentration on determinations made in the urine collected immediately before the animals were killed. This is one of the factors involved in the calculation of the work of the kidney, and insofar as the morning urine did not truly represent the urine of the 24-hr period, our estimates of work are in error. In spite, however, of all these shortcomings, we consider that all the results taken together establish beyond reasonable doubt the thesis we have presented

In our general plan we undertook to measure the factors concerned in the urea work of the kidney (rate of urea excretion, urine urea, and serum urea concentrations) 40 days after the removal of 0%, 25%, 50%, and 75% of the kidney and also to measure the amount of protein in the kidney, thus obtaining simultaneous observations on the structural as well as the functional effects of the removal of renal tissue. The

experimental methods have already been described (page 72). In addition to this, we decided to make these observations under three distinct dietary conditions designed to induce three different levels in the amount of osmotic work required of the kidney. In the first of these, the rats, after operation, were kept on the same stock diet on which they had been reared. This is a mixture of ground wheat, ground soybean, cornstarch, and alfalfa, to which 10% of crude casein is added along with sardine oil, sodium chloride, and bone ash. It contains 17.2% of protein. It is entirely adequate for growth and maintenance. Our desire to eliminate complications due to vitamin or mineral deficiency induced us to keep this stock diet as the base for the other two diets, therefore we got the second diet by adding 50% of air-dry ox liver to 50% of the stock diet. This liver was prepared by pulping fresh liver, removing gross connective tissue and large vessels, and drying at 80° C in a current of warm air. The third diet was obtained by adding 50% of commercial casein to 50% of the stock diet.

In order to avoid deaths from uremia on the high protein diet (page 273), we used female rats that were 70 days old. None of the animals died, and all seemed to be healthy 40 days later when they were killed, but the following table shows that their growth rates were influenced by the operation and by the differences in protein consumption. (Table 46)

TABLE 46

% of kidney removed	body weight at operation gm	body weight at kill gm	% change in body weight after 40 days
STOCK DIET			
0 0	123 2	161 2	+30 8
26 05	131 1	164 5	+25 5
50 25	126 4	161 5	+27 8
75 80	130.4	158.9	+21 9
LIVER STOCK DIET			
0 0	117 0	154 4	+32 0
25 8	127 8	161 2	+26 1
48 7	123 4	156 3	+26 7
75 2	123.4	134 9	+ 9.3
CASEIN STOCK DIET			
0 0	118 7	153 4	+29 2
29 62	119 5	159 3	+33 3
50 20	124 8	144 0	+15 4
75 7	121 6	132 0	+ 8 6

These body weight changes are calculated from the averages of groups that usually contained ten rats. There were fifteen such groups for the stock controls on which a sham operation without removal of any kid-

TABLE 47

URea Work 40 Days After Reduction in Kidney Size

% kidney removed at operation	number rats	body weight at kill gm	kidney weight corrected to 150 gm body weight mgm	kidney protein corrected to 150 gm body weight mgm	Concentrations: serum urea mgm per 100 cc	Concentrations: urine urea mgm per 100 cc	$\frac{U}{B}$ urine urea concentration / serum urea concentration	urea rates: urea excretion per 24 hr mgm	urea rates: urea excretion per gm kidney protein per 24 hr mgm	work rates: work per 24 hr cal	work rates: work per gm kidney protein per 24 hr cal
STOCK DIET											
0.0	144	161.2	984.5	157.9	35.3	6,125	174.9	363.2	2,205	15.58	94.6
26.1	20	164.5	833.0	128.4	43.7	4,284	97.2	365.2	2,666	13.53	99.0
50.4	35	161.5	774.2	120.1	52.0	4,377	86.1	422.4	3,390	14.95	119.2
75.8	31	158.9	664.0	95.4	66.4	3,191	48.3	348.1	3,524	10.58	107.1
LIVER STOCK DIET											
0.0	90	154.4	1,226.2	196.7	44.4	7,315	150.5	579.5	2,879	24.80	122.9
25.8	30	161.2	1,111.7	172.6	50.3	5,540	111.3	608.5	3,359	23.30	128.8
48.7	30	156.3	1,047.3	155.6	65.7	4,352	66.3	576.2	3,600	19.20	119.8
74.8	30	134.9	770.7	111.3	75.8	3,579	47.2	458.4	4,388	13.60	130.2
CASEIN STOCK DIET											
0.0	90	153.4	1,226.3	191.7	67.1	8,937	119.8	1,063.0	5,478	43.80	225.4
26.3	30	159.3	1,085.0	168.2	77.8	7,180	92.3	1,076.2	6,172	39.30	225.4
50.2	30	144.0	953.0	142.7	100.7	4,880	48.9	1,057.5	7,627	31.73	225.7
74.8	33	132.0	779.0	112.5	143.9	4,538	32.2	889.5	8,623	22.90	222.7

Figure 53, parts *A*, *B*, and *C*, the results are plotted against the percentages of the amounts of kidney protein found when no part of the kidney had been excised, and the data are presented in this form in Table 47.

TABLE 48

FUNCTIONAL CHANGES 40 DAYS AFTER REDUCTION IN KIDNEY SIZE[a]

% kidney protein	% serum urea	% urine urea	% urine urea / % serum urea	% urea excretion per gm kidney protein	% work per gm kidney protein
STOCK DIET					
100 0	100 0	100 0	100 0	100 0	[illegible]
81 3	123 7	70 0	55 0	120 9	[illegible]
76 2	147 3	71 7	48 7	153 7	[illegible]
60.4	188 2	52 2	27 6	159.9	[illegible]
LIVER STOCK DIET					
100 0	100 0	100 0	100 0	100 0	[illegible]
87 8	113 3	75 5	74 0	116 7	[illegible]
79 2	168 0	59 5	44 1	[illegible]	[illegible]
56.6	173 0	49 0	31 4	[illegible]	[illegible]
CASEIN STOCK DIET					
100 0	100 0	100 0	100 0	100 0	[illegible]
87.8	116 0	80.3	77 0	112.6	[illegible]
74 5	150 0	54 6	40 8	[illegible]	[illegible]
58 7	214 5	50 5	26 9	[illegible]	[illegible]

[a] Values expressed as a percentage of the quantities found at kill when no kidney protein was removed.

The less the kidney protein, the higher do the serum urea concentrations rise and the lower do the urine urea concentrations. The rate of urea excretion in milligrams per 24 hr does not ... except for fluctuations explicable on the ground of varying food ...

tion as modified by the concentration changes, tend ... urea excretion ... ney size is reduced. But when the work is expressed ... the kidney ... of kidney protein, thus uniting in one expression the ... per gram functional and the structural changes, the graphs ... both the *constancy, so that after 40 days the combined result approxim...* is that the amount of work done per unit of renal ... change irrespective of how much kidney had been removed ... the sa...

This, however, is to deal with the question on ... 53). When we consider the work done per gram of kidney ... diets, as given in the last column of Table 48, we ... the unit of kidney increases as the protein consu... ...e

TABLE 50

AVERAGE PROTEIN PER NEPHRON AND AVERAGE WORK PER GAMMA OF NEPHRON PROTEIN UNDER ALL DIETARY CONDITIONS

NEPHRON NUMBER LEFT	TOTAL PROTEIN FOUND AFTER 40 DAYS	PROTEIN PER NEPHRON AFTER 40 DAYS	PROTEIN PER NEPHRON % OF VALUE WITH 61,000 NEPHRONS	WORK PER NEPHRON AFTER 40 DAYS	WORK PER γ NEPHRON PROTEIN AFTER 40 DAYS	WORK PER γ NEPHRON PROTEIN % OF VALUE WITH 61,000 NEPHRONS
	mgm	γ		1/10,000 cal	1/10,000 cal	
61,600	182 1	2.97	100 0	4 60	1 549	100 0
46,200	156.4	3.45	116 3	5.84	1.703	109 3
30,800	139 5	4 56	153 6	7.21	1.582	100 6
15,400	106 4	7 08	238 4	10 37	1 465	94 6

This mode of expression has the advantage that it dissociates the functional and structural changes and allows us to see what would have been the effect of the concentration changes on the work of the kidney if the size of the nephrons had remained constant. When we compare Figure 54 with Figure 55 it will be seen that the increase in urea excretion per nephron is relatively greater than the increase in the amount of work per nephron The difference is due to the decrease in the value of the ratio between the concentration of urea in the urine and in the serum as the nephron number decreases (Table 49). When the number is most reduced, the urea excretion per nephron is 3½ times increased, whereas the work is increased by less than 2½ times. As a consequence of the change in the $\frac{\text{urine urea}}{\text{serum urea}}$ concentration ratio, the remaining nephrons are saved 113% of the work done when all of them are in operation. This is the purely functional part of the total adjustment of the kidney to a decrease in size.

If now we take our protein determinations and calculate the protein content per nephron, we find that the nephrons have an increasing protein content as their number decreases, and when we calculate the work per unit of nephron protein, thus including both functional and structural changes, we find again, of course, as is shown in the last column of Table 50, that an approximate constancy is attained. But again we have to admit that these figures are in some degree illusory because the nephrons do not only increase in size; they change qualitatively as well as quantitatively, and the qualitative factor—the disproportionate increase in the size of the proximal tubule—we cannot measure.

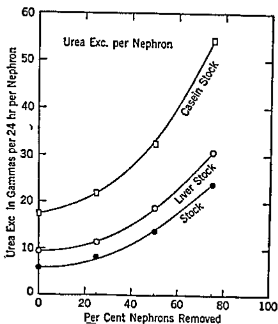

Urea Exc. per Nephron
Casein Stock
Liver Stock
Stock
Urea Exc in Gammas per 24 hr per Nephron
60
50
40
30
20
10
0
0
20
40
60
80
100
Per Cent Nephrons Removed

Fig 54

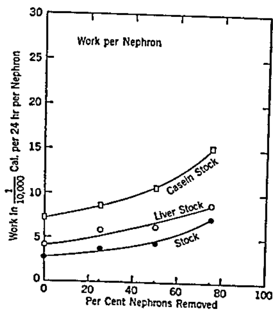

Work per Nephron
Casein Stock
Liver Stock
Stock
Work in $\frac{1}{10,000}$ Cal. per 24 hr per Nephron
30
25
20
15
10
5
0
0
20
40
60
80
100
Per Cent Nephrons Removed

Fig 55

stance, to look for some neural mechanism through which any loss of renal tissue would constitute a signal for an augmented blood supply to the remainder. If that could be demonstrated we might ascribe the growth of the kidney to increased nutrition, and an increase in the glomerular filtration volume per nephron might help us to comprehend the lowering of the urine urea concentration. Apart from the fact that no such reflex mechanism has as yet been found, and that direct measurements of the rate of blood flow through quarter kidneys failed to show an increase (76), we do not believe that the hypothesis of growth from increased nutrition is able to account for the observed facts. This increase in size of the kidney remnant is a very special sort of growth, not determined by the nutritional conditions that determine growth in general, and is governed by factors that are quite specific (77). We know there is one substance, urea, that makes the kidney grow, though it has no effect on the growth of other organs. Urea has this effect when given directly or indirectly through the increased urea formation that follows an increase in protein consumption. No doubt there are other such substances. A huge increase in the creatinine concentration of the plasma, long enough continued, might have this effect. If it did we should know how it came about because we could explain the growth as a consequence of increased osmotic work. Furthermore, we know the shape of the curve of growth induced by an increase in nutrition. It is an S-shaped curve that at first rises slowly, accelerates, and then decelerates. The shape of the curve of growth induced by the removal of renal tissue is altogether different, for at first it rises quickly, and the growth rate after the first day steadily decreases (page 65). We know this curve, too. It is the curve of growth from "work hypertrophy."

Even though it has not been directly demonstrated, there is almost certainly a later increase in blood flow to the kidney that is decreased in size. The growth of the glomerulus is very probably stimulated by the stretching of its capillaries by a greater flow of blood, and a stretching of Bowman's space by a greater volume of filtrate. Indirectly, this probability is made much stronger by the results of renal blood flow measurements derived from diodrast clearances. But this may be a result, not a cause, of growth. The enormous flow of blood through the kidneys—one-third of the supply for the whole body—is necessary because the kidney has to produce an enormous volume of glomerular filtrate, and we have every reason to suppose that its blood supply goes far beyond the need of the kidneys for nutrition. There does not seem to be any clinical situation, outside of extreme shock, in which the kidney suffers from anoxia caused by an insufficient blood supply. Everyone who has worked with renal vein blood knows how red it is. In a series of uremic

patients who were very anemic, we failed to find any anatomical or functional evidence of improvement in their renal status when we removed the anemia by intravenous injections of red blood-cells. Their hearts improved but not their kidneys. So, for these and for other reasons, we think the hypothesis that the kidney grows after it has been reduced in size because it gets more blood is inadequate.

HYPOTHESIS THAT THE OBSERVED CHANGES ARISE FROM CHANGE IN BLOOD COMPOSITION

The curve of the rate of growth of the kidney whose size has been reduced by operation is identical with that of the intact kidney following an increase in protein consumption (page 237). This circumstance seems to make it possible to enlarge the consideration of the mechanism of this growth beyond the particular conditions of the experiments we are discussing, and to see these conditions as examples of a more general situation. If we do that, we can neglect the circumstances connected with the operative removal of part of the kidney and consider what, outside the kidney, might give the initial stimulus for its growth. We are obliged to do that because in this second example the kidney itself is not directly altered.

There are two ways in which extrarenal changes can influence the kidney. The central nervous system has connections through which the growth rate might be altered, but there is no evidence that a severance of these connections alters the size of the kidney, or that stimulation of the renal nerves has any measurable effect on the rate of growth The other possibility is that changes in the composition of the blood supplied to the kidney might alter growth. It is in the blood that we must look if we are to understand how such extrarenal events as the greater or lesser introduction of protein into the gastrointestinal tract can make the kidney grow large or small The only constant connection we have found is that when more protein is consumed and the kidney grows larger, the blood urea concentration is raised, and, conversely, when little protein is taken and the kidney atrophies, the blood urea concentration is lowered. There can be little doubt that this blood concentration change is a major initial reason for the change in the kidney. In the other case, when a part of the kidney is excised, a decrease in urea excretion is doubtless the primary effect, but it is invariably followed by an increase in blood urea concentration. We can say that blood urea concentration changes always precede any change in kidney size, whether as a consequence of an increase in urea entering the body, as when more protein is eaten, or as a consequence of a decrease in urea leaving the body, as when the number of nephrons is diminished.

Since this is so, why should we not be content to accept change in

How are we to imagine that this one small part of the kidney establishes its rule over all other parts? Only, it seems to us, by hypothecating a constant relation between its size and the amount of energy it uses for its work—a relation such that with every increase or decrease in that energy the resulting disequilibrium between the size of the structure and the energy it expends is in itself the stimulus to an atrophy or hypertrophy of its mass. This, however, would only be the first of a whole series of integrated relationships between this structure and all other elements of the kidney. We know that these are not directly proportional relations, and there is reason to think that the degree to which any particular structure of the kidney waxes or wanes when the osmotic work is changed is dependent on the degree to which it contributes to the work. We know, for instance, that with increase in work it is the proximal tubule that becomes most enlarged. But the glomerulus also grows, the vessels enlarge, and doubtless in the end even the fibrous tissue stroma is increased, but each part in its own degree.

Although insofar as structural changes are concerned, we can thus derive a hypothesis from our experimental facts that serves to relate them to one another and, in an approximate manner, to explain them, the functional changes are still unaccounted for and largely unexplained. We may, it is true, suppose we understand on mechanical grounds how the blood urea changes might be brought about, but such considerations are wholly inadequate for the urine urea concentration changes. Now there is a limit, rough and ill-defined to be sure but statistically very definite, to the capacity of the kidney to produce urine whose urea excretion exceeds a certain value (78). When we were considering various functional measures in relation to their ability to serve as a basis for the prediction of the amount of functionally active renal tissue, we found that a directly proportional relation existed between the amount of kidney protein and the urine urea concentration when measured under conditions that induced a high rate of urea excretion, presumably because under these circumstances this limit was approached, and some degree of uniformity was thus imposed. Now we suggest that this functional restriction has an anatomical basis, and that it arises from the limitations of the structure directly concerned with the removal of water from the urine. This process is one in which water is transported from a concentrated urine to a relatively dilute blood, and the degree of work involved depends on the number of times the urine is more concentrated than the blood This number is the $\frac{\text{urine urea}}{\text{blood urea}}$ ratio which unites in one expression both the blood and urine concentration changes. The relation which we think is the determining one is that which exists be-

tween the concentration ratio and the mass of the concentrating structure, though all we can measure is the total renal mass.

With this we return again to osmotic work as the end which unifies and co-ordinates all that happens, functional as well as structural, for the work done is only the rate of excretion modified by the concentration ratio value. Because the osmotic work of the kidney directly rises and falls with the number of molecules of urea in the urine, any change in the rate of urea excretion is associated with an approximately equal change in energy used by the concentrating structure—a change which, if continued, is the prelude to an atrophy or hypertrophy of the structure until the equilibrium between mass and energy is restored. This is the fundamental reason for the changes in the size of the kidney in which all its elements, in varying degree, take part. In addition we suppose that the behavior of the concentration ratio—its decrease, for instance, when the kidney mass is decreased—is a consequence of the nature of the concentrating mechanism, arising either from limitations in its structure or restrictions on the energy it can command, which render it incapable of separating water from urine that is more than a certain number of times more concentrated than the blood. This is the fundamental reason for the functional changes we have measured. It is only the other aspect of the same process through which the structural effects are brought about. Function and structure cannot be separated.

The discussion of these experiments has been prolonged to a perhaps wearisome degree, it has been full of intricate detail, and in the end it has become almost wholly abstract and hypothetical. But in this case it was required of us that we carry the analysis of the data to the furthest possible limit because the conditions we chose reproduce many of the signs and symptoms we find in patients with glomerular nephritis, and we consider that the results thus constitute a crucial test of the validity of the therapeutic principle of rest from osmotic work. When the work per nephron is increased by a reduction in nephron number, though the growth of the kidney stops when only half the lost tissue has been restored, we find that the work per unit of nephron protein is in the end no greater than when the full number of nephrons was in operation, because the combined effect of the structural increase and the decrease in the concentration ratio eliminates the excess load of work. Although the precision of this result is marred by our inability to measure the actual concentrating structure, we submit that all of the observed facts can be most simply related and understood if we adopt the hypothesis that we are dealing here with a homeostatic system of regulation, involving anatomical as well as functional factors, all integrated toward the

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given; nevertheless 38% of the rats with bigger and better kidneys died in uremia while all the others survived (page 275). This second error, therefore, is like the first.

To think that renal structure and function can be considered apart from the demand for work is not essentially different from supposing that glomerular nephritis can be understood apart from the patient. Both are consequences of isolating in thought certain aspects of disease that can be comprehended only when they are seen as elements in a total situation. This sort of abstract thinking is apt to occur in medicine only when we have to act without direct observations of our own to guide and correct us. It is prevalent in the treatment of glomerular nephritis because we have been content to use secondhand information derived from other people's work. We do not fall into this error when we are dealing with situations with which we are familiar and where we feel at home. No one, for instance, would tell a patient with a recent cardiac infarct that he should make a practice of running uphill because that is the way to make his remaining heart muscle fibers bigger and stronger.

Today, glomerular nephritis is almost universally treated by measures that impose a more than ordinary load of work on the kidney. This fact is in itself enough to show that the anatomical effects of increased work which, in a rather vague way, are already part of the general knowledge common to all clinicians, have not been taken as a compelling argument in favor of a form of treatment that will give rest to the kidney. Nevertheless we feel that the functional effects of increased work, as demonstrated in the experiments we have just discussed, should suffice to give pause to the exponents of the modern method of treatment, particularly if they are considered in conjunction with the structural changes. Let us, however, recognise that, quite properly, there is only one final argument in therapeutic discussions, the argument from clinical results. On this account there may well be some natural impatience with a presentation that, through such long and devious indirections, continues to avoid the main issue. But no other way is open. For to be in any way convincing an argument based on clinical results must have a scientific setting, at least a division of patients into two groups, one given a just adequate amount of protein with lots of water and the other a high protein diet with little fluid. But that is impossible. For once it has been decided that some particular strategy is best there is no longer freedom to experiment and the same general plan will be used for every patient without exception. So here no sudden change in treatment can be won by frontal attack. If it comes it will come slowly and by indirection, through by-passing and undermining the stronghold of tradition with

the interstitial edema, and the arterial lesions *separate and apart from* the kidney? Do they not do more than simply destroy it? Are they not effective in changing the mode of action of the kidney? And are these structural changes in the kidney not dependent on the blood sent from the heart? Are they not influenced by every change in protein metabolism? There is no such thing as glomerular nephritis by itself. We can distinguish only a specific modification of a human being, something that belongs to *him* and acts on *him*, but something, also, on which all else within him acts. There is nothing here completely new and self-contained. *The laws that govern the maintenance and growth of structure* and the operation of the functions of the body are still in effect. The disease has only changed the *conditions under which they act.*

The assumption that the disease is a parasite on the body and that it has its own laws is the first error in the argument we are criticizing, but there is an analogous error concealed within what seems to be the inescapable logic of the therapeutic conclusion. For it is true that the disease destroys a large part of the kidney, that the patient is dying on this account, and that we could save him if we could give him new kidneys. Since we can't do that directly, why should we not do it indirectly? If we give him a lot of protein, his remaining healthy renal tissue will grow larger and will be *functionally more effective.* Nevertheless, if, not seeing the error in the argument, we proceed to put the prescription into effect, the patient will grow worse, not better, and will be in danger of death from uremia. The error is the supposition that the patient's future depends entirely on the quantity and capacity of his renal tissue, whereas in fact it is equally dependent on the demand for work we impose on what kidney he has left. All the experimental work we have described says that we cannot attach any significance to isolated measurements of the structure and function of the kidney. Thus it is useless to ask what quantity of renal tissue is proper for a rat of 150 gm body weight. We find averages that vary from one another by as much as 74% *(page 56)*. *It is absurd to ask what level of urea concentration is to be expected in rats whose kidneys are entirely normal,* because the answer is that it may be anywhere between 5 and 500 mgm per 100 cc. That answer, which is the only one we can derive from the facts of observation, is of no use to anyone. The meaning of structure and function lies not in themselves but in what is required of them. *It is only when the work of the kidney is given that its size begins to mean something or that its functional manifestations acquire significance.* When a high protein diet is given to young rats from which three quarters of their renal tissue had been excised, it is true that the remaining kidney grew larger and did more work than when little protein was

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knowledge achieved in fields where experiment is possible. This does not mean that we cannot be more direct than we have been hitherto. In the experiments we shall now describe the measurements are clinical and the results are given in terms of therapeutic effect.

Experiments on the Treatment, by High and Low Protein Diets, of Rats with Hypertension, Anemia, Increase in Blood Urea Concentration, Decrease in Urine Urea Concentration, and with Proteinuria and Cylindruria

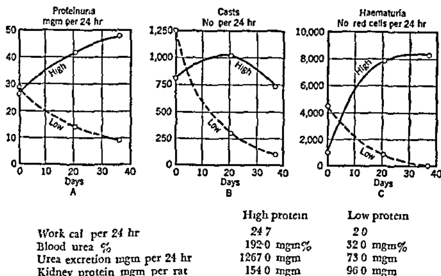
The results in Table 47 (page 244) show that the greater the protein consumption and the smaller the number of nephrons the higher rises the blood urea concentration and the lower falls the urine urea concentration. As the load of work increases we thus find developing in greater and greater degree two signs of renal failure with which we are already familiar in our patients. But these are not the only indications that our rats are sick in much the same way that our patients are sick. Their hearts, for instance, become hypertrophied as the work increases. This cardiac enlargement is due, we think, to an increase in diastolic pressure, for in rats whose kidneys had been reduced to a quarter of the original size Chanutin and Ferris found, on direct cannulation of the carotid artery, that the mean arterial pressure was often raised to markedly abnormal levels (79). Again, as we watch our patients, we are familiar with the fact that as their renal function fails they become anemic. This sign also we find in our rats, and again in proportion to the added work we have imposed on their kidneys. When we look at their urine there is the proteinuria and the increase in the rates of excretion of casts and cells that we observe in our patients. These rats are suffering from the cardinal signs and symptoms of patients with chronic nephritis. If we are not able to help them by resting their kidneys, we certainly have no right to propose such a method for our patients.

From rats 75% of their kidney was removed when they were 70 days old, and they were left on the stock diet (17% protein) for 40 days. Then the rate of protein and of cast and cell excretion was measured, and they were divided into two approximately equal groups. One was given a high protein diet with an adequate vitamin and mineral content (86% air-dry lactalbumin) and the other a low protein diet (5% lactalbumin) obtained by substituting cornstarch for the lactalbumin. The results obtained 20 days later and the observations made when they were killed 40 days after the treatment was started are shown in Figure 56.[a]

This is not a good therapeutic experiment. The low protein intake

[a] This figure is reproduced, by permission, from a paper in the *Transactions of the Association of American Physicians*, 55 225, 1940.

was too low and other conditions were far from optimal. Thus, a greater differentiation might have been obtained if we had added salt to the low protein diet and removed it from the high in order to get a marked difference in water as well as protein consumption. But it suffices to dem-



	High protein	Low protein
Work cal per 24 hr	24 7	2 0
Blood urea %	192 0 mgm%	32 0 mgm%
Urea excretion mgm per 24 hr	1267 0 mgm	73 0 mgm
Kidney protein mgm per rat	154 0 mgm	96 0 mgm

Fig 56 The quantity of renal tissue was reduced to 25% of its original amount and the rats were maintained on a diet containing 17% of protein for a period of 40 days. They were then divided into two groups These two groups were given diets identical in caloric, fat, mineral, and vitamin concentration, but one was a high protein diet (86%) while in the other cornstarch was used to replace the major portion of the protein so that its protein content was low (5%) In the three graphs the rates of excretion of protein, casts, and red blood cells found in these two groups are given at 0 days just before high- and low-protein diets were started, as well as the rates measured on two other days during the next 40 days The figures given below the graph represent measurements made just before or after the groups were killed 40 days after the diets were started.

onstrate that we can improve the condition of small-kidney rats by giving them little protein and can make them uremic by giving them a lot of protein. When we come to discuss the treatment of the initial stage of glomerular nephritis we shall give another therapeutic experiment with results that are, in a certain sense, even more decisive.

Effect of High and Low Protein Diets on Rats with Masugi Nephritis

At this point the objection will properly be raised that the situation we have to deal with in our patients is qualitatively different from that in the rats. Glomerular nephritis is a disease, and a very peculiar one, and

so we have no right to suppose, simply because the symptoms arising from a simple reduction in nephron number are ameliorated by rest, that the same effect would be obtained in our patients. We accept the objection as logically valid and admit that the results of these experiments fall far short of a direct demonstration that rest is good for patients with glomerular nephritis. But those to whom this sort of objection seems peculiarly cogent should note that rest from osmotic work will not only benefit rats whose kidneys have been reduced in size by operation, it will save the lives of rats whose kidneys have been damaged by disease. The so-called "Masugi" nephritis is a disease of animals that resembles glomerular nephritis in man in that, *under ordinary conditions, it often* tends to continue and progress until it leads to death in uremia. Farr and Smadel (80) were not interested in the osmotic work of the kidney, but in the course of an investigation of other questions they compared rats with this disease kept on a low protein diet with others kept on a high protein diet. Though they refrain from drawing any therapeutic inferences, their results are clear. On the low protein diet all the rats were markedly improved or wholly recovered, whereas all the rats that were given a high protein diet quickly died in uremia. In this case, *at least, the outcome of an active and continuing renal disease is determined* by the amount of protein that is consumed,—a result that should interest those who advocate a more than adequate protein intake.

Comparison of Casein and Liver as Sources of Food Protein; Possible Effect in Food of Nitrogen-Containing Substances that Are Not Proteins

All of the experimental work we have cited validates the view that osmotic work is the specific work of the kidney. Viewed as a whole, it is possible to see *all the individual changes in structure and function* as elements in a single system of relationship that moves as a whole in response to change in the demand for osmotic work. The thesis that rest may be beneficial in the treatment of glomerular nephritis in man is thus strongly supported But the support is neither direct nor specific. We can derive from it only the most general indications as to the quantitative objectives to be sought for in our dietetic treatment. As to the sort of protein we should use, we get no guide. In fact, the reader has probably noted that within the framework of the observations we *have been discussing there is an unresolved discrepancy* on this point. Since this may prove to be a matter of crucial importance in the actual management of patients, we reproduce the data derived from rats on the 50% liver stock diet and compare them with the data from rats on the 50% casein stock diet (Table 52).

TABLE 52

COMPARISON OF EFFECT OF LIVER STOCK AND CASEIN STOCK DIETS ON THE KIDNEY PROTEIN CONTENT AND UREA WORK OF THE KIDNEY

	KIDNEY PROTEIN		UREA WORK	
operation % removed	liver stock mgm	casein stock mgm	liver stock cal per 24 hr	casein stock cal per 24 hr
0	197	192	25	44
25	172	168	23	39
50	156	143	19	32
75	111	113	14	23

What we see here is that the quantity of protein in the kidneys of the liver stock rats is as large as in the casein stock rats, although the urea work done is much less. This disproportionately large size of the kidney on the liver stock diet is not to be explained by the work we have measured. Presumably it is related to substances associated with the proteins in liver that do not exist in casein. The work measured in these experiments was that needed for urea excretion, and this urinary constituent was measured because urea is the only substance present in large amount in the urine that has to be concentrated. But here we are depending on what the physical chemists tell us, and they speak only of the minimal amount of work needed and say nothing about "friction." Now 50% of this liver stock diet consisted of whole dried liver, and this contains an array of non-protein nitrogen containing substances whose nitrogen, at least, the kidney excretes, as well as compounds of protein combined with nucleic acid, hæm, and polysaccharides that may give rise to urinary constituents other than urea. Though none of these may be present in large amount in the urine some may require for their excretion an expenditure of energy out of proportion to their quantity. This, however, is pure speculation. The question as to what sort of protein-containing foods we should give our patients can, as far as we can now see, be brought to a decision only by the laborious method of measuring the effect on the structure and function of the kidney of various crude food proteins. On this work we are now engaged.

Up to this point in this chapter we have been engaged in a wholly academic discussion. We have presented theoretical and experimental evidence that leads to the conclusion that in the treatment of renal disease, as in the treatment of cardiac or joint disease, we should be ruled by the conception that cessation from work—the bringing about of conditions that lead to relative rest—should be our central and determining therapeutic principle. In diseases of the heart or of the joints no laborious argument is necessary. The direct experience of patients as well as of doctors is enough. But in disease of the kidneys no well-

There is nothing out of the ordinary to be found on examining his heart and lungs and abdomen. His fundi show no abnormality. There is no doubt, however, that his blood-pressure is 135 systolic and 90 diastolic. The urine voided at 6 A.M. that day is inspected, and it certainly looks like coffee. It is now 12 noon and he has not passed any urine since then, so we ask him to collect urine into a clean bottle. This specimen has exactly the appearance of the 6 A.M. sample. After a little persuasion we succeed in getting his blood and oxalate part of it at once. The rest of the physical examination is done when we get back to the office. The hematocrit tube is filled after thorough remixing of the oxalated blood, and 5 min later we see that he is apparently somewhat anemic, for the red cell volume is only 80% of normal. The buffy layer of white blood-cells and -platelets on the top of the red cells is a little thicker than usual but the plasma is quite clear. The protein concentration in the serum is 6 gm per 100 cc. In the meanwhile the office nurse has shown us the color of the serum 6 min after the addition of alkaline picrate. It is a deeper orange than usual and indicates a concentration of 2.5 mgm of creatinine per 100 cc. The volume of the 6-hr urine is only 60 cc or 240 cc per 24 hr. The specific gravity is 1 015. The 15 cc of urine, after centrifuging, has a deposit of nearly 0.5 cc of closely packed, brown material, above a clear, port-wine-colored urine. When this sediment is diluted with salt solution sufficiently to let us see any detail, it is seen to consist in the main of disintegrated and fragmented red cells, but among them are many colorless cells. The ⅙ of 1 hr urine, in this case only 2 cc, has also to be diluted before we can make a count. Then we find that on a 24-hr basis the number of red cells is about 2,000,000,000. We cannot be sure of exactitude, however, because so many of the cells are fragmented. But there is no doubt that there are 500,000,000 of what are, presumably, tubule cells, though there are also some cells that may well have once been polymorphoneuclear leukocytes. There are certainly only a few casts, not more than 10,000 per 24 hr, so that we may have to look over a large area and examine a series of drops from the diluted urine before we find any. When we come across one it is the typical blood cast of the initial stage—a cylindrical clot in which we can see the faint outlines of tubule cells among the agglutinated reds. The 1 cc of supernatent urine that represents 1/10 of 1 hr urine, when diluted to 7 cc with water and then to 14 cc with acid phosphotungstic, gives us, after 5 min centrifuging, a volume of 0 3 cc of precipitate. This represents a 24-hr excretion of 2.5 gm of protein, a concentration of more than 1 gm of protein per 100 cc of urine. As a result of all these observations we make a diagnosis of glomerular nephritis in the initial stage. It is likely that the disease is not much more than 24 hr old. We then

return to the patient's house to plan his treatment, taking with us a copy of the food tables.

HOME MANAGEMENT

The first question is whether he shall be treated at home or taken to the hospital. The answer given by practical experience is that he can be more efficiently managed at home. In part, this decision depends on economic considerations. His father makes $150 a month and has no savings. The cost of really adequate hospital treatment that might give the dietetic control needed is hopelessly beyond his capacity even though the doctor were to charge nothing for his services. But would not less luxurious service be adequate? Once he gets to the hospital, any diet thought proper can be ordered, the floor nurses will keep an eye on the boy, the hospital laboratory will report on the urine. If any complication should arise, all the apparatus of a complete diagnostic and therapeutic organization are available—the x-ray consultants, the bacteriologists, and the surgeons all standing ready for service in case of need. In the hospital the child will be safe and the cost need not be more than $5 00 a day. But if these considerations lead, as they usually do, to hospitalization, the clinician will have lost real control. For such a case as this, these impersonal services are inadequate. It is no criticism of a hospital dietetic department to recognize that, as a rule, all it can do is to provide the number of grams of protein, calories, and so on that the doctor orders. The dietitians do try to meet the food likes and dislikes of their patients, but they have not got the time or the staff necessary to find out how much is taken by each patient. So we are only deluding ourselves if we suppose that it is enough to write an ideal diet on a chart. The only thing that matters is what the patient actually eats and drinks, and without special nurses that essential knowledge cannot usually be obtained in a hospital. There is only one person who can take the time and has the devotion needed for this task. That is the child's mother. She can work only in her own home. Therefore, for reasons that are more than economic, we shall decide to treat the boy at home.

The next question is how to obtain the co-operation of the mother and the boy. Now at present the mother knows that something is wrong, but she does not know what it is, and the boy feels perfectly well and wants to get up. Strict commands may suffice for the moment, but it is more effective, and in the long run will be necessary, to explain the situation. The coffeelike urine is something they can see. They can be told that this indicates that the kidneys are at the moment badly damaged, almost as damaged as the boy's leg would be if a truck had run over it. It might be said that kidneys do not hurt because they cannot feel,

know already that this minimal rate of urea excretion can only be attained under conditions that are unphysiological. Everyone who has studied this question knows that the minimum nitrogen excretion cannot be approached unless the food protein consumption is reduced far below the amount needed for maintenance, let alone growth. Before we go any further, it is well to recognize that the conflict between theory and practice exists for what we called the first as well as for the second theoretical requirement. We can only obtain what is demanded by all the theoretical and experimental evidence we have adduced by making a choice between what is best for the nutrition of the body as a whole and what is best for the kidney. We might, of course, play both ends against the middle and decide to give just enough protein to satisfy the demands of the body and still get a reduction in protein consumption that would represent a great lightening of the demand for work from the kidney. In practice we have rejected this compromise. Our reason is wholly practical. It rests on recognition of the clinical facts that indicate that, in this patient, at this time, the need of the kidney is vastly more important than the need of the body. We therefore break the rules that must be followed for adequate protein nutrition. But we recognize that, since direct clinical experiment is precluded, any such proposal should properly arouse an attitude of most critical skepticism. Nothing less than results obtained under the closest possible reduplication of the conditions that exist at the beginning of glomerular nephritis can be admitted as valid for a decision as to the rationality or irrationality of an admittedly unphysiological method of treatment, and, no matter how decisively in its favor may be the experimental results, no more than a cautious and anxious clinical trial will be justified.

EXPERIMENTS ON THE EFFECT OF DIETS OF VARYING PROTEIN CONTENT, INCLUDING THOSE DEFICIENT IN PROTEIN, IMMEDIATELY AFTER A REDUCTION IN NEPHRON NUMBER

We cannot induce in animals the exact structural renal changes that we find in the initial stage of glomerular nephritis. The nearest approach would be the so called "Masugi" nephritis, and we have already cited the results, if not the conclusions, of Farr and Smadel. But the sudden functional effects of the renal lesion can be duplicated. One of the most unique features of glomerular nephritis is its almost explosively sudden onset. The glomeruli become obstructed and the function of the nephrons diminished so quickly that it is almost as though they had been excised. The parallelism is maintained immediately after the initiation of the lesion, for the form of the decline in the intensity of the pathological process, as measured by the decreasing rates of excretion

of protein, red cells, and tubule cells (page 192) is an inverse pattern of the rate of growth of the remaining fragment after removal of three-quarters of the total renal mass (page 66) and is like the curve of the rate of increase in the amount of effectively functioning renal tissue that occurs immediately after the onset of glomerular nephritis in man (59). All these curves are similar, in that the rate of change is at first very rapid but sharply decelerates as time elapses until it becomes asymptotic to the abscissa. There is thus reason to think that the closest approach, and certainly the only quantitatively precise approximation, to the sort of situation with which we are faced at the onset of glomerular nephritis is through the excision of a large proportion of the kidney by operation, a mechanical reduction of nephron number.

In the experiment we shall now consider, we are looking for evidence as to the clinical effect of a variation in protein consumption which includes quantities so small that they are insufficient for body maintenance and induce a negative nitrogen balance. In addition, we want to make our observations after an operation by which all but a quarter of the total kidney is excised and at a rather short interval after the operation, because no clinician would give a diet inadequate in protein for any great length of time. We took 30-day-old rats for this experiment because young animals show greater changes than adults with variation in the protein concentration of their foods after partial nephrectomy.[7] After removing 75% of their kidney from eighty-six of these small rats, we divided them into three groups and put them on three diets from which they could all get adequate calories, vitamins and minerals, but which contained different concentrations of protein. The first group got food that contained only 3.7% of protein as lactalbumin. On this diet young normal rats lose weight and cease to grow because they cannot get enough protein. The second group got food containing 22.6% of protein, a concentration on which the rate of growth approaches a maxi-

[7] Young rats are more likely to die of uremia after a great reduction in nephron number than are older rats. When the vena cava is tied above the entrance of the renal veins, the venous pressure in the kidney rises so high that the formation of urine ceases. Whether the animal recovers or dies in uremia will depend on the rate of formation of new venous channels through which the blood from the kidneys, which now has to run down the vena cava, can flow from the pelvis into veins running up the abdominal wall to the heart. We found that all 30-day-old rats, after a transient uremia, recovered from this operation, but as older rats were used there was an increasing mortality until, with the oldest groups, 90% died of uremia (81). Therefore, the high death rate in young rats after partial nephrectomy does not arise because their vascular system is less capable of adapting itself to change. The reverse is true. Nor is it a consequence of any lack of capacity to restore lost renal tissue (82). We believe the high death rate in young rats, after the removal of three-quarters of the kidney, when a diet with a high protein concentration is given, follows because their food consumption per unit of body or kidney size is greater than in adult rats. Their protein consumption is larger and thus a relatively greater load of work is required from their remaining nephrons.

mum.[8] The third group got food containing 64.1% of protein. All t three diets were isocaloric, and the protein variation was obtained substituting lactalbumin for cornstarch. The observations made a we after the operation are summarized in Table 53.

TABLE 53

EFFECT OF CONSUMPTION OF VARYING AMOUNTS OF LACTALBUMIN DURING ONE WEEK FOLLOW THE REMOVAL OF THREE-QUARTERS OF THE KIDNEY

		BODY WEIGHT			
group	protein eaten gm per day	body weight original gm	body weight final gm	% body-weight change	urea excretion mgm per 24 hr
1	0 31	52 5	51.3	− 2	41
2	1.67	48 7	50 9	+ 5	102
3	2.38	48.3	32.4	−33	402

group	serum urea % mgm per 100 cc	serum creatinine % mgm per 100 cc	urea work cal per 24 hr	kidney protein (corrected)[9] mgm
1	29	1 10	0 8	34
2	65		2.5	37
3	274	4 02	6 0	42

The first group given the 3.7% protein diet consumed 0.31 gm o protein a day. This was a quantity inadequate for growth and even fo maintenance, for they lost weight in spite of taking considerably large amounts of food than the other two groups. The urea excretion wa very low, the serum urea and serum creatinine concentrations were not high, and the amount of urea work was small. The second group did not eat as much, but with a diet containing 22.6% of protein they got enough protein for adequate nutrition and more than enough of all other requirements and thus gained 5% in weight. But their serum urea concentration was 65 mgm per 100 cc and their remaining frag-

[8] Pediatricians seem, quite generally, to regard as "optimal" for children that protein consumption which induces the most rapid growth. There is reason to suspect that rate of growth may be an inadequate criterion of what is best, or that at least it is one that should be tested by observation of what happens to the individuals who are trained to take 3 or 4 gm of protein per kilogram of body weight after they pass into age groups in which there is no longer any pediatric observation Slonaker's data (83) show that, in rats, a protein intake that gives the most rapid growth in youth gives rise to adult rats that in the end are smaller, die sooner, and in many other respects are inferior to rats given amounts of protein below the quantity required to induce the highest possible growth rate.

[9] The weights of kidney protein were corrected for the final differences in body weight by multiplying the observed weights by the factor $\frac{50^{0.75}}{B.W.^{0.75}}$. No correction system is free from objection in a situation such as the one we deal with here, in which the experimental conditions give rise to differences in the composition of the body weight arising from variation in the proportions of protein, fat, and water in the bodies of the three groups

are compa

any other we

altered even

per 100 gm of body weight is used.

ment of kidney had to do nearly three times more work. The third group, on the 86% lactalbumin diet, though they ate only 40% as much food as the first group, got much more protein than they needed. They were all uremic rats when they were killed, with an average serum urea concentration of 274 mgm% and a serum creatinine of over 4 mgm%. Their quarter kidneys were doing 7½ times more work than the first group on the absolutely deficient protein consumption.

The account given in Table 53 of what happened to these three groups of rats is incomplete because it deals only with the condition of the rats that survived. The mortality rates given in Table 54, showing that with a deficient protein diet all of the animals recovered, that with an optimal protein consumption 13% died, and that when a high protein diet was taken 38% died, provide additional evidence that is equally distinctive and even more final. They died of uremia. We proved that by showing that the urea content of the tissues of some that had very recently succumbed was over 500 mgm per 100 gm of tissue.[10] In another experiment in every respect similar to the high protein diet of this series except that casein was the protein source instead of lactalbumin, the average serum urea concentration of the survivors was 320 mgm per 100 cc, and there was a 47% mortality rate. We conclude that under these conditions the diet that contained an inadequate amount of protein gave the best clinical results.

TABLE 54

RATE OF DEATH IN UREMIA WITHIN 7 DAYS FOLLOWING REMOVAL OF THREE-QUARTERS OF THE KIDNEY ON AN INSUFFICIENT, OPTIONAL, AND HIGH LEVEL OF PROTEIN CONSUMPTION

GROUP	PROTEIN % IN DIET	% MORTALITY
1	3 7	0
2	22.6	13
3	64 1	38

If diets deficient in protein are better than those containing an adequate quantity of protein, may not one that contains no protein at all be best? We obtained these conditions by giving 5% dextrose as the sole nutrient. At this low concentration of sugar the animals are able to approach a sufficient caloric intake only by drinking so constantly that in 24 hr they consume an enormous amount and sometimes excrete a volume of urine equivalent to more than their body weight. To avoid any possible complications from vitamin deficiency we added 1% of a B-complex syrup made from rice polishings. In this way we succeeded in reducing the urea work to 0.4 cal per 24 hr, less than half the work done

[10] When we say that these rats died of uremia we do not say what it was that poisoned them. It was certainly not urea, but we suppose that the degree of retention of urea is an index of the degree of retention of an unknown substance that kills.

not yet been validated. At least, such experiments suggested obs tions it would be worth while to make in man. They led us to a of the effect of diets containing very small and inadequate amoun protein in people with intact renal structure and function, who in good health. We have measured the rates of excretion and the and serum concentrations of urea and creatinine. This work is no completed. One fact, however, that has a bearing on the treatmen the initial stage of glomerular nephritis is already established. We that 4 to 5 days after the institution of diets adequate in calories, mins, and minerals, the urea and creatinine work of the kidney is same, whatever the quantities of protein we give, so long as they ren between 0.0 and 0.2 gm of protein per kilogram of body weight. *reason for this uniformity* is not apparent, but the fact cannot questioned.

This, however, brings us only one step nearer to the solution of clinical problem. We have reason now to believe that any prolon zero protein diet would be bad *not only for the patient but for his* k neys, and the experiments on normal individuals over a short time s gest that a little protein would be better than none. But we still do have the information we need. We know almost nothing about the b ance between protein anabolism and catabolism at the very beginning glomerular nephritis. This information can be obtained in the scar fever wards of city hospitals. It is needed because, for all we kno a patient at the beginning of glomerular nephritis may have the sa incapacity to use protein for anabolism that Cuthbertson and others ha found in many patients after fractures or bone operations (84). If th state exists, any protein we give will increase the work of the kidney.

These gaps in our theoretical comprehension of the situation do n preclude treatment. Practical considerations have priority in the actu *handling of the clinical situation. Here is an 8-yr-old boy who weighs* kilograms. All we know about his renal state and about nutrition enjoi an adequate caloric, vitamin, and mineral diet that contains a minim amount of protein. We know that in normal people 0.2 gm of protein pe kilogram of body weight imposes no more work on the kidney than n protein at all. Even though in the case of our patient it may be found tha no protein would, theoretically, be the best prescription, there are prac tical reasons that make that impossible. It needs a good deal of resolutio for an adult to swallow enough pure carbohydrate and fat to cover his cal oric needs. So, in any case, we *shall have to give some protein.* For ou 20-kilogram patient 0.2 gm of protein per kilogram is only 4 gm, and thi *is about the smallest amount* we can give and still get a diet that an 8-yr old boy will eat. So we tell him and his mother that we want him to take

as little protein as possible but as many calories as he wants. We tell them what protein is and ask them to look at the protein content of foods as given in the tables in the Appendix. They note that sugar, oils, jams, jellies, and many fruits contain little or no protein. But these are supplementary foods. What is needed is a starch substrate that will serve as a nutritious vehicle for all their tastes and flavors. So we ask them to look under "Cereals" and note that cornstarch, arrowroot, and tapioca are practically free of protein. These are usually made into puddings with milk, but milk has 3% of protein, so a substitute must be found. Fruit juices may be used or, better still, diluted pastry cream. This has 40% fat and not much more than 1% protein. When it is diluted to eight times its volume of water, it has the same fat content as milk and very little protein. With this diluted cream, enough cornstarch pudding can be made for the whole day, and any housewife will know better than any doctor how to make it seem that every time it is served it is a new dish. One time it appears as hot chocolate cornstarch pudding, next as a frozen mold with half an apricot with cream, and so

TABLE 56

EXAMPLE OF A 6-GM PROTEIN DIET

TIME	FOOD	AMOUNT (standard cup and spoons)	PROTEIN gm	CALORIES
7 A.M.*	Orange juice	½ C	0.3	48
	Puffed rice	1 C	1.0	72
	Jelly	1 t	0.0	35
	Cream (40%)	¼ C	1.0	226
	Sugar	2 t	0.0	40
10 A.M.	Pineapple juice	½ C	0.3	64
1 P.M.	Lettuce	1 leaf	0.1	2
	Celery	3 stalks ¾″ × 5½″	0.0	4
	French dressing	1 T	0.0	135
	† Cornstarch	1 T	0.0	36
	† Raspberry juice	1 C	0.0	88
	† Sugar	3 t	0.0	60
	† Lemon juice	1 t	0.0	2
	Ginger ale	¾ C	0.0	65
4 P.M.	Grapefruit juice	1 C	0.9	76
	Graham crackers	2	1.0	70
	Butter	1 t	0.0	36
7 P.M.	Hot baked apple	1 small	0.0	60
	Sugar	4 t	0.0	80
	‡ Cornstarch	1 T	0.0	36
	‡ Cream 40%	¼ C	1.0	226
	‡ Sugar	2 t	0.0	40
	‡ Chocolate	1 t	0.0	21
	‡ Pineapple juice	1 C	0.7	128
			6.3	1650

* This breakfast should be varied by selecting other cereals low in protein and other fruit juices or fruits.

† The cornstarch pudding should be varied by using other fruit juices and chopped fruits.

‡ Or the pudding can be made by some of the other recipes and the cream and chocolate given as a cup of hot chocolate.

disease in which the treatment of the kidney as such should be given priority over all other considerations for it seems likely that what happens within it during the first few weeks will be decisive. We therefore should not pass abruptly from 6 or 8 gm to an adequate amount, but should make additions step by step in quotas of a few grams every few days, depending on the rate of improvement, until just enough for maintenance but not for growth has been reached. Sherman (5) has shown that 0.5 gm per kilogram of body weight is, on the average, sufficient for nitrogen equilibrium in adults. We have no data for 8-yr-old boys, but 0.75 gm per kilogram, which in his case would be 15 gm of protein, should certainly suffice. By this time all the work is being done by the boy and his mother. It takes only a few minutes to make sure that his blood-pressure is now about 85 systolic and 65 diastolic, to tell them how the urine is improving, and once a week to get a sample of blood, look at the total protein and caloric consumption, and say what may seem advisable about an increase in the protein. Details can now be safely left to their own ingenuity, from which there is sometimes much to be learned. Arrangements will now be made with the school so that the boy can go on with his lessons at home, and after the first few days in bed the mother should be shown how to give him a massage three times a day, to be followed by systematic exercises with his legs and arms while he lies in bed.

The next question that will be raised is, "When can he get up?" We have a wholly empirical rule that he should remain in bed until the rate of epithelial cell excretion has fallen to not more than 10,000,000 cells per 24 hr, but obviously the decision involves other factors in the urine and blood and in the situation as a whole. We know that when he does get up there will be an increase in the rate of protein, cast, and cell excretion. But now we are leaving the initial stage and beginning to enter the latent stage, and as we do that we must consider more and more the general health of the boy and be less influenced by purely renal considerations. We cannot wait until hematuria has gone. That will not be until the renal lesion has healed or the boy is dead. The slight increase in cast, red cell, and protein excretion that we will observe when he gets up are probably due to man's relatively recent acquisition of the erect posture. In the upright position the circulation through the kidney may not be quite so smoothly accomplished. In this case when the epithelial cell excretion has reached the 10,000,000 level, when for 2 weeks, at least, his blood-pressure and blood urea concentration have been normal and his protein excretion is 0.2 gm or less, we let him up for gradually lengthening periods during the day. We do not believe that any attention should be paid to the rate of red cell excretion, nor do we think that the

extent of the lesion is a determining factor. In this case the creatinine concentrations on the first, third, fifth, and seventh day of the disease were 2.5, 3 5, 3 0, and 2.5 mgm% and the blood urea concentrations 60, 100, 75, and 65 mgm%. On the fourteenth day they were 2 mgm% and 50 mgm% and on the twenty-first, 1.8 mgm% and 30 mgm%. This indicates an extensive lesion, one which has probably rendered functionless more than 50% of the nephrons, but it seems to us that it is the intensity of the lesion rather than its extent that should be the deciding factor in answering this question.

COMPLICATIONS

In some patients seen at the very beginning, the original streptococcal infection still carries on in one form or another, so that we have a patient who has a continuing middle-ear disease, an empyema, or a spreading cellulitis. In all such cases it is in the hospital rather than in the home that ever-present help and relative safety is to be found, because intensive penicillin or streptomycin treatment and, if necessary, prompt surgical intervention, have priority. Under these conditions it may happen that for weeks the patient has not been able to take enough protein and, if that is the case, the dietetic problem is transformed from an endeavor to give as little protein as possible into an attempt to give enough, and this in spite of the fact that the intensity and extent of the renal lesion may be quite similar to that of the patient we have been considering. As a basis for this opinion we have, again, to appeal to experimental results.

In rats maintained previously on a diet that was in every respect adequate, we have shown that the rate of restoration of renal tissue during the first 5 days after the removal of one kidney was not altered by a variation in protein consumption induced by giving diets that contained from 1% to 57% of protein (85). This is, in fact, one of the experimental reasons, in addition to those already given, why we feel that an inadequate protein intake is justifiable at the onset of glomerular nephritis. But this capacity to enlarge the remaining nephrons, even when almost no protein is consumed, is strictly limited in time, for when rats of the same age and size were given the 1% protein diet for 10 days before 50% of the nephrons were excised, the rate of restoration was very definitely lessened. This effect, shown in Figure 57, presumably arises because, when the kidney is removed from an animal that has had an adequate amount of food protein up to the time of operation, there are amino-acids available for immediate repair even though no more reach the body from the gastrointestinal tract. When, however, the operation is preceded by protein starvation, these resources have been

fibrin threads would probably not be observed. If we had not seen him in the initial stage, we should have asked him to get a concentrated and acid urine in order to confirm the diagnosis. In this case the urine would still be too dilute if he were simply to follow the rule of abstaining from fluids after his breakfast until he collected the night urine next morning. He is taking 3,000 cc of fluid a day, and it would be necessary to keep him on, say, 1,500 cc for 1 day and then get him to concentrate on the next. We should not even then obtain a urine with a specific gravity of 1.032, which would be about the average in normal boys. It would probably be about 1.025. The night urine volume expressed as a 24-hr rate would be about 480 cc. The 4 cc of this thoroughly mixed urine, representing ⅕ of 1-hr urine, gives, grossly, more sediment than is ordinarily seen.

After the supernatant fluid has been pipetted off until only 0.5 cc is left above the sediment, a drop of this thoroughly mixed volume transferred to a blood counting chamber presents a unique picture. At first glance under the low power one gets the impression that there has been an accidental contamination for, here and there, fine, faintly yellow threads that twist and interlace with one another are seen. These are fibrin threads and indicate that at least in some glomeruli there is still an inflammation so acute that fibrinogen is leaking through from the plasma in the glomerular capillaries and clotting when the molecules come close enough together in the concentrated urine of the lower reaches of the tubule. If the movable stage is now used, there will probably not be many fields to cover before an orange-colored cast comes into view. If the high power is turned on this cast, it will not show the textbook picture of a blood-cast, for there will be no recognizable red cells to be seen. There is a conglomeration of irregularly shaped clumps of deep-yellow or orange-colored material. It is not like the typical cast of the initial stage, which is a mixture of epithelial cells and clumped masses of red cells. Here there are usually no epithelial cell remnants. This is the blood cast of the latent stage. It is a clot of blood held together by fibrin threads which cannot be seen, but it is an old clot in which the red cells have broken down and agglutinated until they are no longer distinguishable. These are the two pathognomonic elements in the sediment. There will also be 100,000 hyaline casts, 70,000,000 red cells, and 2,000,000 epithelial cells per 24 hr. The protein excretion is low, only 0.10 gm per 24 hr. There has thus been a pronounced shift since the initial stage. At that time the sediment indicated a marked tubular, as well as glomerular, damage. There were hundreds of millions of tubule cells, and the blood-casts had almost as many tubule cells as red cells Now, the blood-casts are pure blood-casts, the rate of tubule cell excretion

is almost normal, the protein leaking from the damaged glomeruli has been almost wholly reabsorbed by the reconstituted tubules, and only these blood-casts, the fibrin threads, and the constant microscopic hematuria are left to indicate the continuance of an active glomerular inflammation.

A DIET WITH A PROTEIN CONTENT JUST ADEQUATE FOR MAINTENANCE AND GROWTH

What, if anything, should be done? The answer given by theory, if not as yet by practice, is quite clear. We must continue to secure conditions under which the minimal amount of work is done by the kidneys within the limits set by consideration of the general well-being and growth of the patient. We have a right to ask for a continuance of care and effort because we have an objective—the complete healing of the lesion and an end to the need for any treatment. We cannot promise success. For example, the initial intensity of the disease may have set up barriers to the adequate nutrition of the kidney in the form of a thickening of glomerular and tubular membranes, which may forever preclude complete healing But we know that more than 80% of lesions do heal, and so we have good reason to hope. The initial stage has, in this case, resulted in the destruction of probably more than half the total number of nephrons through the permanent cessation of the flow of blood through the glomeruli, and one factor that will determine the fate of those that remain is the amount of osmotic work they must do in eliminating the end products derived from the food the patient eats. We are giving him 15 gm of protein a day, but per nephron this is equivalent to 30 gm for a boy who has the full number left. He has enough for maintenance. The question is whether that is enough for growth The answer is given by serial body weight measurements We have seen children grow slowly on as little as 0 5 gm of protein per kilogram of body weight, not the "optimal" growth of pediatricians but a steady, slow gain.

If the protein is to be thus limited, the nature of the protein to be given becomes a question of some importance. In our experiments on rats we have been impressed, perhaps overimpressed, with the apparently excessive amount of work done by the kidney in excreting the end products derived from the consumption of meat, kidney, and liver. This is indicated by the greater enlargement of the kidney, induced by protein contained in these foods, than is found when cereal or milk proteins are given (page 265). It is results such as these that lead us, in the case we are now discussing, to advise against taking meat, fish, chicken, liver, or kidney, and especially to be careful never to allow meat

extracts, meat soups, or broths. The reason why the latter should be excluded is obvious. They contain no protein except a little gelatine and are essentially hot-water extracts of meat containing urea, creatinine, creatine, and a multitude of other known and unknown nitrogenous derivatives. To take them has much the same effect on the kidney as the ingestion of concentrated urine. It has been objected that to cut out meat, fish, and chicken is dangerous because vegetable and cereal proteins have a low biological value. This is not necessarily true under our conditions because biological values usually have been determined by measuring the utilization when the food in question is almost the sole source of protein. On a mixed diet containing milk, egg, cereal, vegetable, and fruit proteins, the amino-acid deficiency in any one food protein may very well be made good by the excess in another. In any case, we have many records of patients that grew well without meat proteins on 0.75 gm per kilogram or even less, and this is the final test. Since that is true, we are determined mainly by the practical consideration that if the patient takes even a small helping of meat he will use up so much of his daily 15-gm supply that the free selection of many other foods will be curtailed.

After 2 weeks of increasing activity at home and 6 weeks from the onset of the nephritis, the boy goes back to school. For the first 2 weeks he goes for only half a day, and when he comes home he reclines on a sofa or on a deck chair in the garden while he does his lessons, plans his diets, or plays with his stamps or planes. The effect on him of these increasing freedoms is determined by having him come to the office after 1 or 2 days at school. He brings with him three collections of urine, the first from 7 A.M. to noon when he was up and about and in school, the second from 12 noon to 7 P.M. when he was lying about the house, and the third from 7 P.M. to 7 A.M. when he was in bed. Even though the urine is dilute, we can find out from the relative rates of protein and epithelial cell excretion whether or not we have been premature. If, for instance, the three successive protein rates are 0.6, 0.25, and 0.1 gm per 24 hr, we are going too fast. If we get 0.2, 0.1, and 0.05 gm of protein and 2,000,000, 1,500,000, and 1,000,000 epithelial cells per 24 hr, we must be cautious about any further extension of freedom but may carry on. If the rates are 0.1, 0.07, and 0.05 gm of protein and 1,000,000 epithelial cells for each of the three samples, we may feel reassured. The patient should see the tubes with the precipitated protein and have their meaning explained because then he comprehends that both he and the doctor are controlled by facts that are not subject to their hopes, fears, or errors. Sooner or later he will be back at school, even though the rates may never fall to levels as low as some of those we have cited.

There will come a time when the general deleterious results of keeping an 8-yr-old boy in a state of inactivity will outweigh any advantages to the kidney that may be derived from the maintenance of a horizontal position.

In many patients as times goes by, it will become impossible to get a readable precipitate of protein, and then the question comes, "Has the lesion completely healed?" It is a hard question to answer because the abnormal fades so gradually into the normal. In his case the last anomaly to disappear will be hematuria. This can be measured with precision only under conditions of concentration, and a number of unit areas may have to be gone over before the few red cells are found which indicate that some trace of the disease still remains. When that time comes, there is every reason for hope. It will not then be regarded as a hardship to continue a regime, that has now become a matter of use and wont.

TREATMENT OF PATIENTS WHOSE RENAL LESION HAS HEALED

What is to be done when we are sure that no trace of the disease is left? We say the lesion has healed, but it is a healing with defect—with a permanent reduction in the number of nephrons. Shall we relax all dietary precautions? If we do, we may expect that youngsters between 15 and 20 yr of age will take from 100 to 150 gm of protein, and if half their nephrons are gone this will impose a burden of work on each remaining nephron that is equivalent to what would ordinarily be required per nephron on a 200 to 300 gm protein diet per day. Of course, the nephrons left will grow larger, but the blood urea concentration will be higher than normal and the urine urea concentrations lower, and it is possible that the train of abnormalities may develop which we find in our small-kidney rats on a high protein diet—the anemia, hypertension, proteinuria, and cylindruria. So we do not think it is safe to let healed patients leave us free and untrammeled. They should go with as precise a knowledge as we can give them of the extent of their lesion, and they should know why a luxus protein consumption is, for them, unwise. This is no heavy burden of knowledge, nor is the prohibition any real deprivation.

GENERAL MANAGEMENT

Approximately one out of every five of all patients seen in the initial stage will not heal, and we must consider what shall be done if that is true of the patient we are following. Two years have gone by, and yet every time the urine is concentrated we find 30,000,000 to 100,000,000 red cells. Every time we allow such a [illegible] urine to stand

for an hour, and collect all the sediment we can from the bottom of the bottle, we can see in the sediment spread on an ordinary slide under cover slips some orange-colored blood-casts. Though the rate of epithelial cell excretion is often within normal limits, from 0.1 to 0.3 gm of protein per 24 hr is always found. We have shown that even after a continuance of the lesion for much longer than 2 yr, healing is possible, and so it is not justifiable to take away all hope of that eventuality. But it is only realistic to set about preparations for a life that may have to be adjusted in conformity with the existence of a renal lesion that will carry on relentlessly to the very end.

The boy is now 10 yr old and weighs 25 k. As his weight increased, he has increased his protein consumption until it averages 20 gm a day so that he is taking 0.8 gm of protein per kilogram of body weight. He has acquired the habit of drinking lots of water so that his urine volume is between 3,000 and 4,000 cc per day. When the weather is warm he automatically increases his fluid consumption so that the urine is always dilute. He has been encouraged to take lots of salt, and he excretes from 15 to 20 gm a day. He swims, but he does not dive or swim under water. He goes for long walks, but he does not run races. He plays baseball but not football or basketball. His rule is not that he cannot run but that he should stop when he begins to get short of breadth. He is not a social outcast on account of his diet, for now he knows his way very well and can go to anyone's table and get just about what he needs by selection. At first he had struggled against the objective demands of the situation. Now they are accepted without thought and without regret. Having attained a state in which the physical requirements are being met without effort and without anxiety, the best contribution we can make toward the consolidation of this attitude of the patient toward the disease is to evidence such complete confidence in him that it almost borders on carelessness. The intervals between visits to the office are lengthened until he is only seen every 3 or even every 6 months, and all that is said should be in terms of easy assurance irrespective of what ups and downs the actual observations may reveal. The only point at which all carelessness disappears is when it comes to the examination of the sheet that gives the week's average protein and caloric consumption, along with the details of a representative 24-hr diet. The boy is thoroughly conversant with the relation between the volume and the protein content of all the foods he takes. It is no longer necessary that he should write it all down every day, but it is essential that for 1 week before he sees the doctor he should carefully measure everything again to make certain that he has not imperceptibly drifted from his standards. To be anxious about the exactitude of his

dietetics is to impress on the patient that if he will only be careful about that one thing, he can be careless about everything else. A child understands that. It is the motto of many of the fairy stories he has been told.

TREATMENT OF PATIENTS IN THE LATENT STAGE WHOSE RENAL LESION IS ACCIDENTALLY DISCOVERED

The treatment of the latent stage in a patient seen at the beginning and trained from the start is, of course, relatively simple. It is otherwise with the patient in whom the initial stage was missed and who comes because someone finds a trace of albumin in the urine. The difficulty is not related to any uncertainty about the diagnosis. A patient may feel perfectly well, and on physical examination show no abnormalities that can be related to a constant slight hematuria, yet, when we survey all the casts he excretes, if we find the typical latent-stage blood-casts he can be regarded as a glomerular nephritic. We can be as sure of that as of any diagnosis we ever make, once we have excluded a streptococcus viridans bacteremia. The uncertainty lies in what is to be done about it. Here is a perfectly well and happy person who knows only that at times there is a little albumin in his urine, but who already has the seeds of anxiety in his mind, otherwise he would not have bothered to have the matter investigated. This problem is so extremely individual that it is perhaps not very useful to bring it up. The solution will vary in every patient and will depend on a judgment as to what the patient can do about his diet without making him overfearful. To attach a name to the condition, to tell him he has nephritis, is not to tell the "truth" because to many laymen that means a rapidly progressive disease that ends in convulsions and death. The name "nephritis" alone is, in some instances, enough to initiate an anxiety neurosis. The patient may have to be brought quite indirectly to an appreciation of the real situation. We are obliged to be very careful, because, aside from general considerations, there is reason to suspect that in some patients with latent glomerular nephritis the initiation of an anxiety state might become a factor in the determination of the end result.

The latent stage is an equilibrium between a continuing loss of renal tissue on the one hand and, on the other, a continuing functional and structural adaptation lightening the load on the remaining tissue. Not infrequently, the first indication of a break in this steady state is a gradual increase in the average blood-pressure level. Now an increase in diastolic pressure increases the work of the peripheral arteries as well as the work of the heart. In watching patients with early hypertension, it is the rule that at first we can see no evidence of arterial disease. That comes later.

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many hyaline and a few granular casts with an occasional blood-cast. But these are minor changes relative to the increase in the rate of excretion of red cells which has jumped from 50,000,000 to 750,000,000. This is the urine of a patient in the latent stage with an exacerbation.

The boy is not alarmed because he has been forewarned. Though the urine is again grossly bloody, he knows that this is not a reiteration of the initial stage, that he will not have to go through the long rest in bed and the reduction in his protein quota again. He knows that as soon as his fever goes the hematuria will disappear.

Patients can be told about exacerbations because the pattern they follow is generally so uniform that prediction is fairly safe. They have no specific etiology. We have seen them in measles, chicken-pox, mumps, and influenza, as well as in streptococcal infections. Indeed, there need be no bacterial or virus infection. They may follow a bad sunburn, an injection of horse serum, a smallpox vaccination, or an operation in a sterile field. In our experience the one factor that has always been present is fever. The hematuria appears with the fever and goes when the fever goes. The curious and interesting lapse of time between the onset of fever and the hematuria of the initial stage does not occur here. Both the hypertension and the brawny edema of the initial stage are absent. The evidence derived from the examination of the urine suggests that there *is a cloudy swelling of the kidney, associated with a marked increase* in the diapedesis of red cells from glomeruli in which some inflammatory activity still exists. As to pathogenesis, the probable guess would seem to be that this is the reaction of an inflamed kidney to the presence in the blood of a foreign protein or of a displaced body protein. Treatment should not be directed particularly to the kidney but toward the removal of whatever agent is responsible for the fever. There is in this case a special reason for avoiding dehydration, but that only underlines a generally accepted principle in the management of all fevers. We did not find that any permanent extension of the renal lesion was induced by the exacerbations we observed (59), and we do not think they determine to any appreciable degree the course of the disease.

The boy quickly recovers from his undiagnosed infection and the urine is again as it was before. He is kept in bed for 1 week after his fever has gone, and he does not go back to school for 2 weeks. Now a new question arises. The initial stage was preceded by a beta-hemolytic streptococcal tonsillitis. It is now November, and the incidence of tonsillitis is rising. Shall his tonsils be removed in order to decrease his chances of getting another streptococcal throat infection? Throughout the initial stage and the early part of the latent stage no tonsillectomy was recommended because we were anxious to avoid anything that might,

The sequence goes from hypertension to arteriosclerosis. Hypertension as such, whether it is a result of vasoconstrictor center hypersensitivity, in which anxiety sometimes plays a part, or is due to a renal lesion, makes *in the end for a loss of the elasticity* and adaptability of the renal arteries. But these are the very qualities essential for structural adjustment. In the constantly shifting battle front within the kidney the renal arteries are the supply lines of the army that fights for life. If in one sector a unit is wiped out, the ranks must be closed by reinforcements of neighboring units. That cannot be done if the roads to the front, already full to capacity, cannot be widened. More specifically, we will not get the increase in blood flow necessary for compensatory hypertrophy if the medium of the renal arteriole is fibrosed and its intima thickened by hyaline. When that happens the whole burden of adjustment falls on function, and the blood urea concentration will rise and the urine become more dilute, initiating, it may be, a gradually increasing anemia and uremia as the latent passes into the terminal stage.

Though there is good reason for care in how we do it, there is no question at all about what must be done. Somehow or other, these people must be induced to reduce their protein and increase their water consumption, and, in the end, they must understand why they are doing it. The amount of protein they take will depend on the extent of the renal lesion. If the serum creatinine concentration is about 1 mgm%, it will not be necessary to go to the extremes we are advocating for our patient who certainly has less than half his nephrons' left. In any case, the great majority of this group are adults in whom a proteinuria is discovered through life insurance examinations, and for them it is easy to get wholly adequate and appetizing diets containing from 0.5 to 0.75 gm of protein per kilogram in accordance with their status.

EXACERBATIONS

Returning to the boy in the latent stage, let us consider what is to be done when we are called to see him because he has a fever. He came home from school in the middle of the day, feeling tired and weak, and did not want to eat his lunch. His mother found he had a temperature of 101° F and sent him to bed. When he is seen at 5 P.M. he has a reddened throat. He complains that he is nauseated and sore all over. His temperature has risen to 103° F. There is no edema. His blood-pressure is unchanged. He and his mother have seen that the timed urine specimen collected between 12 noon and 4 P.M. is definitely pink, as though it contained blood. We find the volume lower and the specific gravity higher than before. The rates of excretion of protein and epithelial cells are four or five times greater than is usual, and we can see

28 mgm% and the serum creatinine 1 7 mgm%. The urine, when concentrated, still showed blood-casts, and there were 40,000,000 red cells, 500,000 epithelial cells, and in the night urine 0.25 gm of protein per 24 hr. Three months later a letter comes from the university hospital telling us he has a bronchopneumonia, which is now clearing under penicillin. They find a very definite proteinuria with many casts, and they have been referred to us by the patient for a history of his renal condition. Later we hear he has fully recovered from this infection and is coming home for a couple of weeks to convalesce. On his return he says he is still rather easily tired but otherwise feels all right. His red cell volume is 80% of normal, there is no leukocytosis, and the plasma is quite clear. The serum protein concentration is 6 5%. His blood-pressure level has not altered, and there are no signs of any residual lesion in his lungs. But there is a marked change in the urine. The sediment shows 500,000 casts, 10% are epithelial or granular and the remainder hyaline, some with cell inclusions. The rate of excretion of epithelial cells has risen to 10,000,000, but there are now only 1,000,000 or 2,000,000 red blood-cells The most striking change is in the rate of protein excretion The precipitate fills 0 5 cc of the centrifuge tube and indicates a loss of 5 gm of protein a day. We must recognize that we now have positive evidence of a change in his renal lesion—a granular degeneration of the tubule cells associated with a serious loss of protein through the urine.

The first question that arises is whether we should show the patient the centrifuge tube that would tell him at a glance that there has been an astonishing increase in the proteinuria. In this particular instance we would not only not let him see the tube, we would take pains to see that no one else told him about it. Nor would we tell his mother, because to tell her would only be an indirect way of telling him We would tell no one. The reason is that telling gains nothing but may lose some of that freedom from anxiety that is an element in the patient's well-being and a factor in determining the rate of progression of the disease. It may seem as though we were here advocating that the patient be deceived, or at least that certain truths be kept from him. That is not the case. What is being concealed is our fear that the change in the urine may indicate the beginning of the degenerative stage, but it is a fear that is concealed, not a truth It is still quite possible that these signs will disappear and everything be as it was before In that event, would it really have been honest to have had the patient look at that tube? To him it would necessarily have been an inescapable brute fact, unmitigated by that doubt as to its permanency and meaning that is given by the physician's experience. Honesty is not easy. It is certainly not achieved

even transiently, delay the architectural reconstruction going on in his kidney. But now certainly there is evidence that stabilization has occurred, and the question becomes real. Nevertheless, in this case we would still do nothing. The boy's tonsils are not enlarged. If he does get another tonsillitis, the worst that would happen to his kidneys would be another exacerbation. If we take his tonsils out, that in itself will very likely give us an exacerbation. Why should we try to escape a possibility by incurring a probability? On the other hand, if he began to get minor sore throats accompanied by adenitis and fever, his tonsils should be removed because then we should have a reason related to his general health rather than his kidney. So we think the answer should be given on grounds that are no different from those decisive for children without nephritis.[11]

Ten years go by. The boy is now 18 yr old He weighs 60 k and takes 35 gm of protein a day. At every biennial examination he is found to be in excellent physical condition. His blood-pressure is 110 systolic and 75 diastolic, and it is only in the urine that any abnormality can be found. But at every examination we find from 5,000,000 to 50,000,000 red cells, and every time a special search is made, blood-casts are found. His scholastic standing is high and he wants to go to the University. At this point he needs some help. A letter must be written requesting that he should not be vaccinated, and arrangements must be made with the dietitian so that he can get the food he needs without having to prepare and cook it himself. We do not discuss with him the various possibilities with respect to the future of his renal lesion, since we cannot predict it with accuracy. There is, first, still a chance that the lesion may heal, but it is a very small chance, second, and most probably, he will carry on in good health for an unspecified period and then very slowly drift toward the terminal stage; third, he may pass into the degenerative stage; and fourth, he may die from some intercurrent diseases or accident.

Treatment in the Degenerative Stage

The course of the disease in the particular patient whose actual treatment we are outlining happened to pass through a degenerative phase which began when he was 24 yr of age. When we last saw him still in the latent stage, he was at the university. He had a natural bent for mathematics and had won a scholarship that enabled him to work toward a Ph D. degree in theoretical physics. His blood-pressure was 100 systolic and 75 diastolic. He had no anemia. His blood urea concentration was

[11] This is a clinical judgment entertained because we have not been able to convince ourselves that the removal of "foci of infection" changed the course of the disease The combination of clinical, bacteriological, and immunological observations initiated by Longcope (61) may yet show that this opinion is in error.

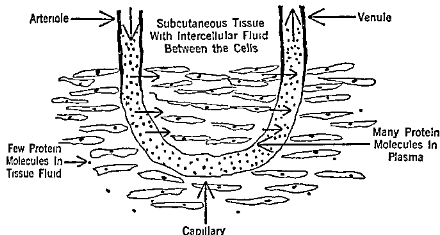


Fig 58. The diagram is intended to show a capillary lying in the subcutaneous tissue The arrows at the arteriolar and venule ends show the direction of the blood flow. The pumping action of the heart imparts to the fluid within the capillary a pressure that is greater than the pressure in the subcutaneous spaces, and the arrows leaving the arteriolar end of the capillary indicate that in this section fluid is passing from the capillary to the tissues But as a consequence of friction the pressure in the capillary decreases and at the venule end is less than the tissue pressure. The arrows entering the capillary indicate that the direction of flow between the capillary and the tissues is now reversed, and the fluid passes from the tissues into the blood stream The intracapillary pressure is the sum of the pressure derived from the heart and the osmotic pressure derived from the circumstance that there are about 7 gm of protein per 100 cc of plasma in the capillary and a considerably lesser concentration of protein in the intercellular tissue spaces. When the plasma protein concentration is maintained at its usual level, the passage of fluid out of the capillary at the arteriolar end and its return into the capillary at its venule end is determined by the fall in hydrostatic pressure within the capillary as it passes from the arteriole to the venule But if the plasma protein concentration decreases, the osmotic pressure of the plasma falls. When the sum of the hydrostatic and osmotic pressures within the capillary at the venule end is no greater than the intracellular pressure, the return flow of fluid into the capillary will stop, fluid will begin to accumulate within the tissue spaces, and the soft, easily pitting edema we find in patients with low serum protein concentrations will appear

a rapid gravimetric determination (86) shows 5 6 gm per 100 cc. There is no longer any question that the essential features of the degenerative stage are gradually becoming clearer and more unmistakable, but this means nothing that appears to the consciousness of the patient, nor has it made any difference in our treatment with the exception of the increase in protein consumption. Holiday after holiday goes by and still there is no essential change, only a very gradual average decline in the serum protein concentration. That becomes the crucial measure, for when it approaches 5 gm per 100 cc, we shall be faced with the problem of the treatment of edema, and as that point is neared the patient should be pre-

by the process, so comfortable to us all, of getting rid by confession of all our wandering fancies. Honesty with patients requires thought and discipline and effort. It has its negative as well as its positive side and involves silence as well as communication. Patients have a right to be very sure that when they ask we will tell them all we know. That is essential if they are to be kept from anxiety. But, while we must share our knowledge with them, we must not ask them to participate in our fears. These are our burdens and we must carry them alone.

RELATION BETWEEN PROTEIN CONTENT OF THE DIET AND PROTEIN LOSS IN THE URINE

But whether this increase in proteinuria is permanent or not, it requires action. This 5-gm loss must be made good in the diet. He is told to take 40 gm of protein instead of 35. In the meantime he goes home to go on with his work, though he does it reclining on a sofa or a deck chair. As the weeks go by, we find that the proteinuria continues at about the same level, even though his anemia disappears and his strength returns, and it becomes more and more certain that he is passing into the degenerative stage. At this time there is no lipemia, and the serum protein concentration is 6 gm per 100 cc, i.e, at a level still within the range of normal variation. There is no change in his blood. There is some increase in proteinuria when he is up and about, but the rate does not exceed 10 gm per 24 hr. He feels perfectly well. Now is the time, before he goes back to work, to tell him that he should every week collect a 24-hr urine, measure the volume, and air-mail an ounce or so to us so that we can follow his protein excretion, and we must explain that this is necessary because since his pneumonia he is losing more protein in the urine than before, and we have to know the amount so that he may balance the loss in his diet. This is still all we know and all we need to say. It may very well be that this is all that will happen and that he will never become edematous.

Three months later he comes home for the holidays. He is in good health and spirits. His protein excretion has lately been averaging 10 gm per 24 hr, and his protein consumption has been raised to 45 gm a day. In the sediment are a number of hyaline casts that contain fat droplets, and there are a few fatty casts and fatty tubule cells. There are fewer red cells than before, and no blood-casts can be found. There is no anemia. The blood-pressure is still the same. The serum urea and creatinine concentrations are unchanged, but the serum has a hazy, opalescent appearance. The copper sulphate method indicates a definite decrease in serum protein concentration. It gives a reading of 5.4 gm per 100 cc. When the fat is washed out of the precipitate with alcohol,

bed, in fact, he is encouraged to go on with his work, except that he is advised to keep his legs up on a chair or sofa as much as possible so that they may not get too swollen and uncomfortable. His average protein loss is later found to be 15 gm per 24 hr. He is still taking 45 gm a day, and his weight without the edema is still presumably 60 k. This means he has available for maintenance only 0.5 gm per kilogram or 30 gm per day, since the 15 gm of protein in the urine has to be replaced His protein consumption is increased to 50 gm because we want him to have some margin of safety. In 4 days his weight has decreased by 8 lb, and there is only a slight edema of his legs at the end of the day. We tell him that there is no reason why he should not resume his usual life. There is, in fact, no essential change in his condition other than that the plasma protein concentration has fallen to a level at which he can be free from edema only if he takes very little salt. His feeling that he is entirely well except for the edema is not a subjective illusion but is supported by all the observations we have made. Edema is a nuisance but not in itself anything to worry about, so that after having made the simple dietetic changes warranted by experience, the best thing to do is to go on with one's life as though the edema did not exist—to accept it and to forget it.

A patient of this type must now be brought to realize that he cannot and should not try to analyze his own pathology. Such self-analysis is natural for anyone with his training. In the initial stage and throughout the early part of the latent stage we have ourselves encouraged him to look at the facts as they are, to subject himself to them and act in accordance with them. But now he is entering a phase of the disease in which a continuation of this attitude would be self-destructive. A consideration of the facts of the disease as they now present themselves to him, or for that matter to us, can eventuate in no further action that is clear and reasonable. It would tend to be a frustrated analysis that might turn inward and, through an intensity of self-observation, bring to consciousness physiological phenomena which might come to be regarded as symptoms of disease. It is not that he is asked to relapse into a childlike faith and hope. For him that would be quite impossible. On the contrary, there is now required of him a much wider and deeper comprehension of the realities of the situation, and at this point, and in his case, this involves a conscious exercise of intelligence and will for the purpose of setting a general direction of internal and subconscious endeavor. The wisdom of a patient grows slowly and in the dark, and, as a rule, the less said about it the better.

We do not tell our patient to take a high protein diet. We do not take an intermediary position, something between the new "high" and

bed; in fact, he is encouraged to go on with his work, except that he is advised to keep his legs up on a chair or sofa as much as possible so that they may not get too swollen and uncomfortable. His average protein loss is later found to be 15 gm per 24 hr. He is still taking 45 gm a day, and his weight without the edema is still presumably 60 k. This means he has available for maintenance only 0.5 gm per kilogram or 30 gm per day, since the 15 gm of protein in the urine has to be replaced. His protein consumption is increased to 50 gm because we want him to have some margin of safety. In 4 days his weight has decreased by 8 lb, and there is only a slight edema of his legs at the end of the day. We tell him that there is no reason why he should not resume his usual life. There is, in fact, no essential change in his condition other than that the plasma protein concentration has fallen to a level at which he can be free from edema only if he takes very little salt. His feeling that he is entirely well except for the edema is not a subjective illusion but is supported by all the observations we have made. Edema is a nuisance but not in itself anything to worry about, so that after having made the simple dietetic changes warranted by experience, the best thing to do is to go on with one's life as though the edema did not exist—to accept it and to forget it.

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pared to accept and in some way understand edema, though what we ourselves know is very little. The essence of it is contained in the diagram in Figure 58.

It is not until the patient is 25 yr old and has become an instructor in the department of physics that we get a telephone call from him. He says that for a week or two he was doubtful, but now he is quite sure that his legs are swollen when he comes back from work at night. In the last few days the edema has been increasing rather rapidly. He wants to know if there is anything he should do. We ask him to take a few days off to let us see what is going on. He comes straight to the office after a 4-hr train journey. There is a soft, deeply pitting edema that extends above his knees. His weight has increased by 15 lb. His blood-pressure is 125 systolic and 85 diastolic. Apart from the edema in his legs, no abnormality is found on physical examination. There is a marked lipemia. The red cell volume is 95% of normal, the blood urea concentration is 25 mgm per 100 cc. The creatinine in a filtrate from his serum is 1.9 mgm per 100 cc. The 5-hr urine collected in the office shows a rate of protein excretion of 20 gm per 24 hr. The sediment indicates a rate of cast excretion of 1,500,000 casts. These are all hyaline casts with fat droplets, except for about 3% of fatty casts. There are no blood-casts, and only one or two rather doubtful red cell shadows are found per unit area. There are 10,000,000 epithelial cells per 24 hr, and 2,000,000 of these are oval fat bodies. Except for the annoying heaviness of his legs he feels perfectly well. By this time we have the results of a gravimetric determination of the serum protein concentration. It indicates 4.9% of protein.

He is told that in this situation he should, for a time at least, reduce his salt consumption. He sits down with his legs up on another chair while the dietitian goes over the salt content of foods (expressed as salt but derived from sodium analysis), showing how he may reduce his salt consumption to less than 1 gm a day.[12] Then he is given some bottles and asked to bring day and night urines for the next 3 days in order that we may get a good average on his protein loss. He is not told to go to

[12] In order to obviate mineral deficiencies of other bases than sodium he takes ½ teaspoonful of the following mixture three times a day in fruit juices:

	Gm
Potassium citrate	115 0
Calcium chloride	3 0
Magnesium chloride	1.0
Manganese chloride	0.5
Iron citrate	0.5
Potassium iodide	0 01

Some patients like to use this as a salt substitute they can sprinkle on their food from a saltcellar.

bed; in fact, he is encouraged to go on with his work, except that he is advised to keep his legs up on a chair or sofa as much as possible so that they may not get too swollen and uncomfortable. His average protein loss is later found to be 15 gm per 24 hr. He is still taking 45 gm a day, and his weight without the edema is still presumably 60 k. This means he has available for maintenance only 0 5 gm per kilogram or 30 gm per day, since the 15 gm of protein in the urine has to be replaced. His protein consumption is increased to 50 gm because we want him to have some margin of safety. In 4 days his weight has decreased by 8 lb, and there is only a slight edema of his legs at the end of the day. We tell him that there is no reason why he should not resume his usual life. There is, in fact, no essential change in his condition other than that the plasma protein concentration has fallen to a level at which he can be free from edema only if he takes very little salt. His feeling that he is entirely well except for the edema is not a subjective illusion but is supported by all the observations we have made. Edema is a nuisance but not in itself anything to worry about, so that after having made the simple dietetic changes warranted by experience, the best thing to do is to go on with one's life as though the edema did not exist—to accept it and to forget it

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We do not tell our patient to take a high protein diet. We do not take an intermediary position, something between the new "high" and

the old "low" protein diet, thus admitting that under these new conditions, when the plasma protein concentration is so low, it might be wise to let him have a moderate amount of protein, not too much and not too little. We hold to our general plan of strategy. Only alterations of a tactical nature are indicated. Now, as before, the maximum possible degree of rest from osmotic work is the objective. For this patient, at this time, 50 gm of protein a day is about as little as can safely be given. To give less would endanger his general nutrition; to give more would be to subject his kidneys to unnecessary work. We cannot add protein to his plasma by adding it to his diet.

The clinical successes that ushered in the era of high protein diets can be explained by considering the conditions under which they were used. That success was achieved in the early degenerative stage of glomerular nephritis with patients who had been subsisting on diets containing little more protein than they daily lost in their urine. Naturally, they grew weak and wasted long before their time because they were suffering from protein starvation. When they were given 200 gm of protein a day they quickly grew stronger and lost their edema. There is no reason to believe that the same immediate results might not have been achieved if they had been given just as much as they needed and no more, and as for the long-time results, we have not been told what has happened to those edematous patients who continued to take 200 gm of protein a day.

HYPOTHESIS AS TO THE RELATION BETWEEN THE CONCENTRATION OF PROTEIN IN THE SERUM AND PROTEIN LOSS IN THE URINE

We have given reasons why we cannot rest satisfied with the view that the decrease in serum protein concentration and the consequent edema is a direct result of depletion through loss of protein in the urine and why it seems necessary to agree that in some cases there is also a defect in plasma formation (page 148), but we should remember that all the convincing evidence we have found in favor of a decrease in plasma protein formation as a primary factor in the production of edema is derived from the observation of patients who certainly did not have glomerular nephritis. We are not willing to agree that in glomerular nephritis a lack of formation of protein is involved, except in a secondary manner. In this disease we find that in nearly every one of the few cases in which we have quantitative information the appearance of the edema has been preceded by a long-continued and large loss of protein in the urine. True, we cannot think of this loss as depleting any fixed "store" of plasma or body protein, because these plasma proteins have a very short life, are continuously being used up in large amounts, and

as continuously are being replaced. But we must hold fast to our clinical facts of observation.

In glomerular nephritis we almost always find the escape of considerable amounts of protein in the urine before there is any decrease in plasma protein concentration. The loss is therefore primary, at least in time. The theoretical difficulty arises because even though the amounts lost seem considerable, it is hard to suppose that they suffice to overtax the capacities of new formation, particularly since we observe that even larger losses incurred through other channels than the kidney are not followed by any permanent lowering of serum protein concentration. Whipple and his group have abundantly shown that losses of protein induced by direct removal from the blood far in excess of the quantities our patients lose in the urine do not suffice to induce edema in dogs (87), and the same observation, directed particularly to this point by Barnett, gave the same answer (88). In men, Bloomfield has pointed out that very large losses due to the removal of ascitic fluid in patients with cirrhosis of the liver do not make them edematous even though their serum protein concentration is already lowered.

Let us accept these observations and agree, provisionally at least, that the loss of protein in glomerular nephritis is too small to account for a permanent lowering of plasma protein concentration. Then we have to ask ourselves, "What is the simplest way to explain the fact that edema nevertheless occurs?" We cannot use here the hypothesis we adopted when discussing pure proteinurias The clinical facts to be accounted for are not the same. In these cases we saw edema develop in a cyclic manner in patients who, in the intervals between their crises, had no proteinuria, and in them there was no preceding, long-continued loss in the urine. In them a single hypothesis—the supposition that there is a defect in plasma protein formation—could account for everything we find; their low plasma protein concentration or edema because the quantity produced is deficient relative to the need, their proteinuria because there is a production of qualitatively abnormal protein molecules either so small that they pass through the glomerular filter in such amounts that the tubule cells cannot reabsorb them completely or so deformed that the tubule cells cannot digest them; and the degenerative renal lesion as a result of too great an accumulation of reabsorbed protein in the tubule cells

If we try to use this hypothesis for the edema that has developed in the patient we are following, we at once find ourselves obliged to make one hypothesis after another, and nothing remains clear and simple. Until the edema appeared, we were relating everything we saw to the structural changes produced in the initial stage, but if we now appeal

to a supposed defect in plasma protein formation, we are predicating an entirely new disease superimposed on his nephritis—one with which it has no visible relation. The essential thing we have to explain in him is not the proteinuria. We can think of that as primarily due to the damage done to the glomerular filtering membrane in the initial stage, and we can understand how the amount of protein he lost in his urine increased after his bronchopneumonia. We can suppose that the cloudy swelling of his tubule cells which occurred during that infection may have initiated a continuing incapacity to reabsorb, as they did during the latent stage, almost all of the protein in his glomerular filtrate. What has to be explained is that edema occurs even though the amount lost is so small relative to what we have reason to believe is his great capacity for new plasma protein formation. We are here only applying to this particular patient the general considerations reviewed in Chapter 7. But in his case we can see the tubule cells full of the hyaline droplets that, by several different methods, have been shown to be the same protein that exists in his plasma, that filters through his glomeruli, and that, in part, escapes in his urine. Now how does this protein that we see as droplets return to the blood? Not as such. Not even, it would seem, in whole molecules.[13] Presumably, that reabsorbed protein returns to the blood stream only after a process of digestion that reduces it to particles small enough to allow passage from the cell into the interstitial fluid and finally into the capillaries of the kidney. It seems to us that it is here we should look for an explanation of the edema. Perhaps failure of intracellular digestion is responsible for the accumulation of protein in the proximal tubule. Perhaps the products of a partial digestion by these cells provide specially available material and stimulus to new plasma protein formation. When that digestion fails, the level of protein formation falls and edema follows. This, of course, is altogether hypothetical, but we do not think it is a useless speculation because it has already suggested experiments, on which we are now engaged, whose results have so far not contradicted it. Still it remains

[13] If molecules of reabsorbed protein did somehow *leave the tubule cell and reach the* intercullular fluid of the kidney, it might be rather confidently anticipated that they would in part be returned to the blood stream by way of the lymphatics. But such evidences as we possess indicates that the rate of flow of lymph from the kidney and the concentration of *protein* in the *renal lymph* are both too small to account for more than a fraction of the amounts of protein reabsorbed. This is one of the reasons why it seems likely that the intracellular treatment of reabsorbed protein breaks it down to less than molecular volumes. The evidence we refer to was obtained in collaborative work between our group and a group headed by Dr Meyer Friedman. We take this opportunity to point out that the statement in the paper (80) that the concentration of urea is higher in *the renal lymph* [illegible]

attempts to measure very small quantities of urea involved a [illegible]

a hypothesis of which the best that can be said is that it enables us to continue to view our patient's disease as a unity and avoid the therapeutic complexities that would be entailed if we were to suppose that he was suffering from two different disease processes.

MECHANICAL REMOVAL OF EDEMA FLUID

A few months later our patient writes that his legs are slowly getting bigger. He keeps them propped up during the day as much as he can, and he gets some help from the use of elastic bandages; nevertheless, as the afternoon wears on his legs ache and are so hard and heavy that it is quite difficult for him to get around. However, he has been able to fulfill all his teaching engagements, his work is going very well, the session is nearly over, and he will be back in a week. When he comes it is seen that he walks very slowly and stiffly because his legs are enormous. The edema extends far up his thighs. Here and there the elastic tissue in the skin has ruptured and striæ have appeared exactly like those seen in the skin of the abdomen of a pregnant woman. The tissues pit deeply, but a good deal of pressure is needed. It is no longer soft; it is now a hard, pitting edema. There is evidently some edema even in his arms, for the blood-pressure cuff leaves a mark. There does not seem to be any appreciable amount of free fluid in his abdominal or pleural cavities. There is no change in his heart action. The blood-pressure is 130 systolic and 100 diastolic. The red cell volume is 90% of normal. The plasma looks like milk or even cream. The concentrations of urea and creatinine in the serum are not appreciably altered. The urine protein rates we have measured during the past 5 months have varied between 10 and 20 gm per 24 hr, but there has been no consistent trend either upward or downward. As a consequence, he is still taking 50 gm of protein a day. Today the urinary sediment presents a picture that, in general, is identical with the one we saw on his last visit. He is in good spirits, justly satisfied because he has been able to do all he had intended in spite of the edema, but naturally also anxious to know if anything can be done to put him in shape for the next session By this time we have the results of the gravimetric determination of his plasma protein concentration. He now has only 4 gm of protein per 100 cc. We still do not know how to raise permanently the level of the protein concentration in his plasma, and until we get that knowledge our therapeutics will necessarily be merely palliative.

In this particular situation, however, we are not condemned to inactivity. We tell him to go home and sit in a chair with his legs hanging down as long as he can. In the afternoon four Southey's tubes are

obliged to reduce the salt intake to the level that is being excreted. We do this unwillingly because, perforce, we have at the same time to accept an increase in the concentration of urea in the urine and a consequent increase in the work required for urea excretion. This increased urine urea concentration is, of course, not directly related to the reduction in chloride excretion, but it follows from the concomitant reduction in urine volume.

The sodium chloride and water held in the rising volume of edema fluid is to all intents and purposes an 0.8% solution of salt, and the concentration is fixed. So, although we cannot give more salt without increasing the edema, why should we not give more water? Is there any reason to suppose that excess water would not be excreted? If it were, would we not have what we want, i.e., a continuing low urine urea concentration without any increase in edema? This is, first of all, a practical question, but it is not one that can be answered without controlled and systematic clinical observation. All we can say is that when we tried to increase the urine volume of edematous patients by asking them to increase their water consumption, we had no success. In theory, the question is already answered in a very instructive paper by J. D. Newburgh (90). He has generalized and extended the von Rhorer equation, of which we made use, and has applied it to situations of the sort we are now discussing. When we were talking about the theory of renal work we dismissed sodium chloride as a urinary constituent of any importance for work because no matter how much we increased sodium chloride excretion, the work involved would always be a negligible fraction of the total work. But when we do the reverse and increase water excretion and keep the salt excretion very low this is no longer true, for then the salt concentration in the blood remains nearly constant, but the concentration in the urine may approach zero and the tubule cells have to work to maintain this now considerable concentration difference. There is thus a theoretical and therefore ultimately a practical limit to a solution of this problem by the method of water administration, though the situation is not clear to us because in rats we were not able to induce an increase in the size of the kidney by this sort of work. Our practice is to take every opportunity to maximize salt and water excretion, trying to keep them in balance, so that the salt concentration in the urine stays within from 0.4% to 0.6%. We are content to have our patients carry around with them 5 or 10 lb more edema fluid than they need have were they always to keep their salt intake at a minimum. As far as water consumption is concerned, we are inclined to think our patients know better than we do how much they should take.

Presumably our rather astonishing ignorance as to the mechanism of the edema of glomerular nephritis is the reason why there is no generally accepted method of treatment. No clinician is so naïve as to regard the relation between edema and plasma protein concentration (page 297) as an adequate explanation of many of the most obvious and superficial facts to be noted in any edematous nephritic. For one thing, this is one of those general rules that are forever leaving us in the lurch in the crucial, specific instance. Everyone has seen the patient who is suddenly and dramatically relieved of his edema, though there has been no increase in his plasma protein or albumin concentration. We may, of course, suppose that if we had a clinical method for measuring plasma volume and so could determine the total circulating albumin, many of these discrepancies would disappear. But the suspicion remains that even then we should have measured only one of the necessary factors, and that the real truth is more complex than we now suspect. For there are even simpler matters that are not clear. Why is the edema fluid present only in the interstices of the subcutaneous tissues and in the body cavities? Tissue spaces containing extracellular fluid exist in the liver, heart, lungs, and brain, but even the patients who have the most extreme anasarca do not have enlarged, edematous livers; their heart action is not embarrassed, no crepitations are to be heard at the bases of their lungs; their sensory and motor reactions are quite unimpaired. Yet the plasma whose abnormally low protein concentration is taken to be the cause of the edema in the subcutaneous tissues is the same plasma that flows through the liver, heart, lungs, and brain. If the low protein concentration were a sufficient cause, we should be prepared to find differences in the degree of edema in different localities but scarcely the waterlogged periphery and the normally dry tissues everywhere else that actually exist. Again, has anyone given a satisfactory explanation of the fact that sodium increases the accumulation of edema fluid? The fact was established by empirical clinical observation. It was not predicted by physical chemists or physiologists. If they understand it, they have not yet been able to make it altogether clear to us. When we come to more fundamental questions, as, for instance, how and where the proteins of the plasma are formed and how and where they are consumed, again we get no answer that is clear and unequivocal. On every side we are surrounded by questions that have to be answered before we can expect to develop a rational therapeutics.

The long-range, negative point of view in the treatment of edema and the adoption as a principle that nothing shall be done that might hurt the kidney is natural and easy for us. We know that this sort of

edema is not to be feared as anything that directly endangers life or seriously disturbs general health. For us the very existence of this symptom is a guarantee that the number of still-functioning nephrons has not yet been too seriously diminished. However, we cannot expect patients to regard their plight in this quite coldly objective light. To many of them it necessarily seems that the edema is the very disease itself, and for some of them it is a calamity that darkens all their life. In the patient we are now following the edema does not matter unless it becomes mechanically disabling. He does not care particularly because his mind is set on other things. In a girl such relative indifference would be unnatural. Even though she may come to be resigned to a treatment that does not go beyond dietetic and mechanical measures, she cannot help pressing for an answer to the question as to how long she must live under the shadow of this affliction. There is no answer to be given. No one can predict with certainty. We can say with complete assurance that a time will come when the swelling will decrease and in the end entirely disappear, but when or how we cannot tell.

Transition from the Degenerative to the Terminal Stage

There now begins for our patient a period of more than 5 yr during which time, to all appearance, nothing decisive seems to happen. The edema carries on. It never again becomes so extreme as to require tapping, but there are times when it is more pronounced and other times when it recedes, though it never quite disappears. His general health has been good, and the edema is so much a part of him that even its fluctuations are taken as a matter of course He is now wholly absorbed in a physico-chemical investigation in which his mathematical capacities are extended to the utmost. Three or four times a year he comes home, and we have an opportunity to continue our observations. Change comes so quietly we cannot tell when it begins. It is only when we plot all our data over these years that we see that there is in every measurement a drift in one direction. His body weight, which is a measure of his edema, fluctuates markedly but on the whole falls year by year, just as on the whole his serum protein concentrations tend to rise. The red cell volumes held around 90% of normal for 3 yr, but during the last 2 yr have fallen so that they are now only about 75%. His serum has become clear or only slightly opalescent. The rate of protein excretion has been more variable than any other measurement, but here too it becomes evident at last that there is a slow and irregular tendency toward a diminution in the loss of protein in the urine. During the past year it has not averaged more than 10 gm a day. On the whole the

intensity of the renal lesion, as measured by rate of cast and tubule cell excretion, has decreased. There are fewer casts and cells. Fatty casts are rare. There are more granular and waxy casts and not so many fat droplets. On the other hand, the red cells are more numerous, and counts that run as high as 30,000,000 are not uncommon. But the most significant of all the observations is the blood urea concentration. Five years ago it was about 30 mgm per 100 cc. Every year the level has risen through 40, 50, 60, and 70 until now it averages about 80 mgm per 100 cc. Yet the general equilibrium of the patient's health is not disturbed. It is true that during the last 2 yr there has been an average increase in blood-pressure. There have been occasional observations running as high as 160 systolic and 110 diastolic, but the heart is not enlarged, there is no evidence of any thickening of the large arteries, and the retinal arterioles appear to be entirely normal.

An optimist confining his attention to the gradual decrease in edema, the disappearance of the lipemia, and the decrease in the rates of protein, casts, and tubule cell excretion might try to maintain that the patient was slowly winning his long battle with the disease. But the realist must recognize that even these apparent improvements are signs that the campaign is being lost. Nephrons that used to contribute their quota of protein, cells, and fat have been converted into fibrous tissue. As they die, the degenerative stage begins to pass into the terminal. With the reduction in the number of nephrons the least damaged surviving nephrons are obliged to undertake an ever-increasing load of osmotic work. They answer as best they may by a hypertrophy which is limited only by irreversible structural changes and by the capacity of the arterioles to bring them materials for growth and maintenance. The index of their relative failure is given in the rising blood urea and creatinine concentrations and the untested but real loss of capacity to produce a concentrated urine. We cannot mistake the meaning of these signs.

Treatment in the Terminal Stage

As our patient passes from the degenerative into the terminal stage, it does not seem to him that anything very noteworthy is happening. It has been a long time since the edema has really bothered him and so he scarcely notices its gradual disappearance. Whenever he comes home he drops into the office as a matter of habit, and as always the same simple measurements are made. He is not curious about the results. He knows they are supposed to be the reason for the slight dietary changes that are ordered from time to time, but further than that he does not go. It would be a mistake to suppose that he consciously di-

to sleep, but even so he often wakens with a bad headache that does not lighten until he has had his cup of coffee and has been sitting straight up for some time. He is annoyed by a taste of ammonia that he can only get rid of with warm salt solution and lemon juice used as a mouth wash. His blood urea concentration is now 200 mgm per 100 cc, the red cell volume is 50% of normal, the plasma is quite clear, and the serum protein concentration is 5.2 gm per 100 cc. The 24-hr urine volume is over 2,000 cc, and the specific gravity is 1.008. He loses on an average of 5 gm of protein a day. In the urinary sediment there are many very pale red cells and from 10,000,000 to 20,000,000 epithelial cells per 24 hr. They are larger than pus cells, and a few of them are quite well preserved, with a clear cytoplasm and a small central nucleus. The fatty tubule cells are gone. When a considerable area of the slide is inspected, it sometimes happens that a very broad, darkly granular, loosely knit renal failure cast comes into view, but very often there are no casts at all

His mother has come to live with him, and they have taken a small apartment just across the street from the laboratory. During the past three months the dietetic problem has been to make the most of the times when he is able to eat. He may, for instance, take a good breakfast and enjoy it, but there comes a wave of nausea and he vomits it all. His mother has a variety of foods constantly ready, and ten minutes later he is sitting down to another breakfast that he may be able to hold. In spite of all these endeavors the days in which he fails to get sufficient calories are becoming more frequent, and as a consequence he is slowly losing weight. Working, like eating, has become a question of waiting for the opportunity. He has won a degree of freedom from subjection to his symptoms so that even when he is very tired and slightly nauseated his attention can be given in large part to the problems that arise in his work, and there are often times when his mind is quite wholly absorbed and he is as keen and penetrating as ever. In his laboratory new apparatus is being designed, but there are uncertainties that have to be cleared away by means of calculations based on measurements made with various subsidiary models. The more laborious part of this work is now done by a younger man with whom he has been collaborating for more than a year. Every day at some time or other he is able to get across to the laboratory to watch operations. He is conversant with every detail and is consulted on the difficulties with which the experimental workers are constantly met. Lately, however, he has grown so tired that he cannot stay for more than an hour or two. In the evening, when his assistant brings the work of the day to him, they discuss only the more fundamental questions related to general strategy.

He must know at least subconsciously that the end is near, and yet there is no indication that he is anxious or at all depressed. He carries on, in no way perturbed.

Finally the day comes when he vomits so frequently that he loses considerably more fluid than he is able to keep down. He is moved to the hospital. Sugar and salt solution are given by vein. The vomiting continues. His face is slightly swollen, almost as it was on the day we first saw him. The urine volume is now less than 1,000 cc, and the sediment shows hundreds of thousands of broad casts—epithelial, granular, and waxy. The blood urea concentration has risen to over 300 mgm per 100 cc. Petechiæ appear on his skin. His breathing is at times Cheyne-Stokes. He is utterly exhausted. Yet on occasion his mind is still alert, and he asks questions about his work. He wants to see the boy with whom he was working. One does not need to be a close observer to know that for him, at this moment, there is nothing he would have other than that which has been and is. It is rather as though he feels a sense of elation and liberation. He sees it all now and comprehends that somehow he has managed to win through to the end without capitulation, and he is glad. He does not give up, but now he recognizes a necessity he does not need to deny because it comes from himself, belongs to him, and gives him freedom. This should be his exit. He should go to sleep.

In the art of anesthesia, as practiced by the obstetrician, there are techniques that can be of value when we are trying to help deeply uremic patients out of this life as smoothly and gently as possible. We want a twilight sleep. Morphine is useful if there is any respiratory anxiety due to cardiac failure, or in the centrally determined polypnoeas that sometimes distress the patient, but as a general anesthetic it probably does more harm than good. It often accentuates the nausea and the itching of the skin What efficiency it has can be maintained only by a very steep increase in dosage, for there is unquestionably a special tolerance for morphine in uremia. The barbiturates given intramuscularly are useful, but in some patients they induce only a dream-troubled sleep. Our experience is that paraldehyde given by rectum is much the most useful drug. An ordinary initial dose would be 20 cc given with 1 oz of starch solution. Occasionally this is not retained, but this difficulty can be overcome by a preliminary wash-out injection of 1% novocaine. Paraldehyde gives a very natural and dreamless sleep. The dose can be repeated whenever the patient shows signs of restlessness, and the quantity given can be safely increased up to as much as 60 cc every 6 hr or so, for here also uremia seems to carry with it a greatly increased tolerance, and there is a wide margin between the

to sleep, but even so he often wakens with a bad headache that does not lighten until he has had his cup of coffee and has been sitting straight up for some time. He is annoyed by a taste of ammonia that he can only get rid of with warm salt solution and lemon juice used as a mouth wash. His blood urea concentration is now 200 mgm per 100 cc, the red cell volume is 50% of normal, the plasma is quite clear, and the serum protein concentration is 5.2 gm per 100 cc. The 24-hr urine volume is over 2,000 cc, and the specific gravity is 1.008. He loses on an average of 5 gm of protein a day. In the urinary sediment there are many very pale red cells and from 10,000,000 to 20,000,000 epithelial cells per 24 hr. They are larger than pus cells, and a few of them are quite well preserved, with a clear cytoplasm and a small central nucleus. The fatty tubule cells are gone. When a considerable area of the slide is inspected, it sometimes happens that a very broad, darkly granular, loosely knit renal failure cast comes into view, but very often there are no casts at all

His mother has come to live with him, and they have taken a small apartment just across the street from the laboratory. During the past three months the dietetic problem has been to make the most of the times when he is able to eat. He may, for instance, take a good breakfast and enjoy it, but there comes a wave of nausea and he vomits it all. His mother has a variety of foods constantly ready, and ten minutes later he is sitting down to another breakfast that he may be able to hold. In spite of all these endeavors the days in which he fails to get sufficient calories are becoming more frequent, and as a consequence he is slowly losing weight. Working, like eating, has become a question of waiting for the opportunity. He has won a degree of freedom from subjection to his symptoms so that even when he is very tired and slightly nauseated his attention can be given in large part to the problems that arise in his work, and there are often times when his mind is quite wholly absorbed and he is as keen and penetrating as ever. In his laboratory new apparatus is being designed, but there are uncertainties that have to be cleared away by means of calculations based on measurements made with various subsidiary models. The more laborious part of this work is now done by a younger man with whom he has been collaborating for more than a year. Every day at some time or other he is able to get across to the laboratory to watch operations. He is conversant with every detail and is consulted on the difficulties with which the experimental workers are constantly met. Lately, however, he has grown so tired that he cannot stay for more than an hour or two. In the evening, when his assistant brings the work of the day to him, they discuss only the more fundamental questions related to general strategy.

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av	average	p	piece
C	cup	r	round
ck	cooked	sc	scant
cu	cube	sl	slice
d	diameter	sm	small
g	grams	sq	square
gl	glass	st	stalk
H	half	t	teaspoon (level)
hp	heaping	T	tablespoon (level)
m	medium	wh	whole
oz	ounce		

FOOD	APPROXIMATE AMOUNT		PROTEIN	CALORIES	SALT
CEREALS AND FLOUR			gm		mgm
Arrowroot	1 T	uncooked	0	60	0
Barley, pearl	3 T	uncooked	3	104	28
Barley, pearl	½ C	ck	3	104	28
Corn meal	2 T	uncooked	2	77	20
Corn meal	½ C	ck	2	77	20
Cornstarch	1 T	uncooked	0	36	0
Cream of wheat	2 T	uncooked	2	68	33
Cream of wheat	½ C or 4 r T	ck	2	68	33
Farina	2 T	uncooked	2	68	33
Farina	½ C or 4 r T	ck	2	68	33
Hominy	2 T	uncooked	2	72	10
Hominy	½ C or 4 r T	ck	2	72	10
Macaroni	3 T or 4 r T	uncooked	4	104	6
Macaroni	¾ C or 8 r T	ck	4	104	6
Popcorn	1 C	popped	2	69	12
Puffed rice	1 C		1	72	13
Puffed wheat	1 C		3	72	30
Rice, brown	3 T	uncooked	2	109	68
Rice, brown	¾ C or 6 r T	ck	2	109	68
Rice, white	3 T	uncooked	2	104	18
Rice, white	¾ C or 6 r T	ck	2	104	18
Rolled oats	3 T	uncooked	3	77	35
Rolled oats	½ C or 4 r T	ck	3	77	35
Shredded Ralston	⅔ C or 50 sq		4	100	33
Shredded wheat	1 large		3	108	33
Soy flour	1 C or 16 T		37	376	?
Tapioca	1 T		0	52	4
Triscuit	1 biscuit		1	32	11
Wheat germ	1 r T		2	37	?
Wheat hearts	2 T	uncooked	4	109	40
Wheat hearts	½ C or 4 r T	ck	4	109	40
White flour	1 C or 16 T		14	453	198
White flour	1 T		1	28	12
Whole-wheat flour	1 C or 16 T		18	507	140
DAIRY PRODUCTS					
Butter, salt	1 T or p 1¼" × 1¼" × ½"		0	108	450
Butter, salt-free	1 T or p 1¼" × 1¼" × ½"		0	108	2
Cheese, hard	1 cu 1" sq		5	74	308
Cheese, cottage	¼ C or 3 T		9	44	146
Cream, whipped	1 T		0	54	5
Cream, 40%	2 T or 1 oz		1	116	10
Cream, 40%	½ C or ¼ pt		2	452	46
Cream, 20%	2 T or 1 oz		1	62	23
Cream, 20%	½ C or ¼ pt		3	248	91
Milk, buttermilk	1 C or ½ pt		8	85	310
Milk, skim	1 C or ½ pt		8	80	310
Milk, whole	1 C or ½ pt		8	170	310
Milk, evaporated, unsweetened	1 T		1	19	19
Milk, evaporated, unsweetened	1 t		0	4	6
Milk, pwd skim	¼ C		8	80	310
Milk, pwd skim	1 T		2	20	64

that the amount of protein taken does not fall below the minimum necessary to maintain health. Protein is the principal chemical material of which living beings are constructed and is the main constituent in meat, fish, chicken, and eggs. It is present also in milk and in large quantity in cheese, which is mainly the separated protein of milk. It exists in varying quantities in all foods except such purified foods as lard, oils, and sugars, and the three prepared cereals—cornstarch, arrowroot, and tapioca.

Calories

The caloric value of foods is a measure of their capacity to provide fuel to run the machinery of the body. The caloric requirement of an individual varies with activity and size.

Salt

Since sodium is the element in salt that should be reduced in the diet of patients with edema, the salt content of the foods has been calculated as sodium chloride from the published data on the sodium content of foods.

There are many condiments that may be used in small amounts to overcome the flatness of a low-salt diet, e.g., allspice, bay leaves, coffee, caramel, cloves, cinnamon, thyme, and vanilla. Commercial salt substitutes should not be used because they contain sodium, and for the same reason sodium bicarbonate should not be taken.

Vitamin-rich Foods

Vitamin B complex	*Vitamin A*	*Vitamin C*
Wheat germ	Butter	Lemon juice
Whole-wheat bread	Egg yolk	Orange juice
Pork	Greens	Grapefruit juice
Eggs	Carrots	Strawberries
Milk	Fish-liver oils	Tomato juice

FOOD VALUES AND MEASURES IN TERMS OF AVERAGE SERVINGS OF FOOD

3 teaspoons	=	1 tablespoon
4 tablespoons	=	¼ cup
8 tablespoons	=	½ cup
16 tablespoons	=	1 cup
2 cups	=	1 pint
4 cups	=	1 quart

A rounded spoonful approximates 2 level spoonfuls.
A heaping spoonful approximates 3 level spoonfuls.

FOOD	APPROXIMATE AMOUNT	PROTEIN	CALORIES	SALT
		gm		mgm
Okra	½ C	2	20	74
Onions	3 m	1	24	30
Parsnips	¾ C or 1 large	2	52	8
Peas, green	½ C or 4 r T	7	76	23
Peas, canned, unsalted	½ C or 4 r T	4	56	23
Peas, dried	⅓ C	7	100	79
Peppers, green	1 large, raw	1	28	76
Pepper, green	1 large, ck	1	20	50
Potato, white	2″ × 4″ baked	2	60	38
Potato, white	2″ × 4″ boiled or ½ C	2	60	38
Potato, sweet	½ C or 2″ × 4″	2	84	66
Pumpkin	½ C	1	24	112
Radish	15-20 m	1	20	175
Spinach	½ C or 4 r T	2	16	152
Squash, winter	½ C or 4 r T	2	32	7
Squash, summer	½ C or 4 r T	1	16	2
Tomato	1 m raw	1	20	30
Tomato	½ C cooked	1	16	20
Tomato juice	½ C	1	20	30
Turnip	½ C or 4 r T	1	24	112
Watercress	2½ C or 1 sm bunch	2	20	251
RECIPES				
Bread, white				
Boiling water	1 C	0	0	0
Lard	1 T	0	135	0
Sugar	1 T	0	60	0
Fleischmann's yeast	¼ cake	0	0	0
Flour	2½ C	35	1132	495
1 loaf		35	1327	495
Pancakes				
Flour	¼ C	3	113	49
Pastry cream	¼ C	1	226	23
Egg, beaten separately	1	6	78	177
		10	417	249
Popovers				
Flour	1 C	14	453	198
Eggs	2	12	156	354
Milk	1 C	8	170	310
Melted butter	1 t	0	36	0
6 Popovers		34	816	862
1 Popover		6	132	145

Add flour to milk and beat well with an egg beater. Then add unbeaten eggs, one at a time, beating thoroughly Add melted shortening Have muffin pans or custard cups very hot, grease well, pour in batter, and bake in hot oven (425° F) 15 min.

FOOD	APPROXIMATE AMOUNT	PROTEIN	CALORIES	SALT
Cake, angel				
Eggs whites	1 C (8-9)	27	108	1152
Sugar	1¼ C	0	1000	0
Flour	1 C	14	453	159
Cream of tartar	1 t	0	0	0
Almond extract	½ t	0	0	0
8 servings		41	1561	1311
1 serving		5	196	164

FOOD	APPROXIMATE AMOUNT	PROTEIN gm	CALORIES	SALT mgm
Soups (canned—meat free)				
Asparagus—Campbell	1 can	7	208	+
Celery—Campbell	1 can	4	155	+
Pea—Campbell	1 can	11	264	+
Tomato—Campbell	1 can	6	237	+
Vegeterian vegetable—Campbell	1 can	7	254	+
Cream of asparagus—Heinz	1 can	8	175	+
Cream of celery—Heinz	1 can	4	303	+
Cream of mushroom—Heinz	1 can	11	304	+
Cream of pea—Heinz	1 can	9	296	+
Cream of spinach—Heinz	1 can	8	375	+
Cream of tomato—Heinz	1 can	5	279	+
Corn chowder—Heinz	1 can	7	293	+
Vegetarian vegetable—Heinz	1 can	11	232	+
Sugar	1 t	0	20	0
Sugar	1 C	0	800	0
Sherbets	1 scoop	2	106	+
Zwieback	2 pc	1	53	+
NUTS				
Almonds	10 m	2	61	5
Peanut butter	1 T freshly ground	4	91	19
Peanuts	18 m	4	95	19
Pecans	10 large	3	226	38
Walnuts	¼ C chopped	4	207	38
Walnuts	6 large	4	207	38
Walnuts	1 r T chopped	1	66	13
VEGETABLES (COOKED)				
Artichoke, French	1 m	2	8	92
Asparagus	8 stalks 4" long	2	20	13
Avocado, raw Fuerte	½ sm	2	262	114
Bamboo shoots	¾ C	3	33	?
Beans:				
Lima, dry	½ C	6	100	50
Lima, green	½ C or 4 r T	8	105	150
Navy, dry	½ C or 3 r T	7	89	53
Mung, sprouts	1 C	3	30	?
String	½ C or 4 r T	2	28	30
Soybeans, dry	½ C or 3 r T	10	101	?
Soybean curd	½ C+	8	80	?
Soybean milk	½ C	4	42	?
Beets	½ C or 2 m or 4 r T	2	36	165
Beet greens	½ C	2	33	?
Broccoli	½ C	3	28	107
Brussels sprouts	⅔ C or 9 m	4	40	8
Cabbage	⅔ C or 5 r T	1	16	46
Carrots	⅔ C or 6 r T	1	28	132
Cauliflower	¾ C or 6 r T	2	20	89
Celery	¾ C or 6 r T	1	16	228
Celery, raw	3 stalks ¾" × 5½"	0	4	96
Celery root	½ C or 4 r T	2	32	35
Chard	¾ C	1	20	218
Corn	½ C or 1 m ear	4	81	68
Cucumber, fresh	½ m or 10 sl	1	16	25
Eggplant	½ C or 4 r T	1	16	45
Endive	2 heads	2	24	276
Horse-radish, fresh	1 t	0	4	0
Lettuce	¼ sm head or 10 leaves	1	16	50
Lentils, dry	½ C or 4 r T	7	100	48
Mushrooms	⅔ C	0	0	68
Mustard greens	½ C	2	28	?

FOOD	APPROXIMATE AMOUNT	PROTEIN	CALORIES	SALT
		gm		mgm
Okra	½ C	2	20	74
Onions	3 m	1	24	30
Parsnips	¾ C or 1 large	2	52	8
Peas, green	½ C or 4 r T	7	76	23
Peas, canned, unsalted	½ C or 4 r T	4	56	23
Peas, dried	⅓ C	7	100	79
Peppers, green	1 large, raw	1	28	76
Pepper, green	1 large, ck	1	20	50
Potato, white	2" × 4" baked	2	60	38
Potato, white	2" × 4" boiled or ½ C	2	60	38
Potato, sweet	½ C or 2" × 4"	2	84	66
Pumpkin	½ C	1	24	112
Radish	15–20 m	1	20	175
Spinach	½ C or 4 r T	2	16	152
Squash, winter	½ C or 4 r T	2	32	7
Squash, summer	½ C or 4 r T	1	16	2
Tomato	1 m raw	1	20	30
Tomato	½ C cooked	1	16	20
Tomato juice	½ C	1	20	30
Turnip	½ C or 4 r T	1	24	112
Watercress	2½ C or 1 sm bunch	2	20	251

Recipes

Bread, white				
Boiling water	1 C	0	0	0
Lard	1 T	0	135	0
Sugar	1 T	0	60	0
Fleischmann's yeast	¼ cake	0	0	0
Flour	2½ C	35	1132	495
1 loaf		35	1327	495

[illegible]

Pancakes				
Flour	¼ C	3	113	49
Pastry cream	¼ C	1	226	23
Egg, beaten separately	1	6	78	177
		10	417	249
Popovers				
Flour	1 C	14	453	198
Eggs	2	12	156	354
Milk	1 C	8	170	310
Melted butter	1 t	0	36	0
6 Popovers		34	816	862
1 Popover		6	132	145

Add flour to milk and beat well with an egg beater Then add unbeaten eggs, one at a time, beating thoroughly Add melted shortening Have muffin pans or custard cups very hot, grease well, pour in batter, and bake in hot oven (425° F) 15 min.

Cake, angel				
Eggs whites	1 C (8–9)	27	108	1152
Sugar	1¼ C	0	1000	0
Flour	1 C	14	453	159
Cream of tartar	1 t	0	0	0
Almond extract	½ t	0	0	0
8 servings		41	1561	1311
1 serving		5	196	164

FOOD	APPROXIMATE AMOUNT	PROTEIN	CALORIES	SALT
Cake, sponge		gms		mgm.
Egg yolk	6	36	468	1062
Egg whites	6			
Sugar	1 C	0	800	0
Flour	1 C	14	453	198
Lemon rind				
Lemon juice	1 T	0	4	2
		50	1725	1262
8 servings				
1 serving		6	214	157
Candy, fudge				
Chocolate	2 sq	10	272	90
Sugar	2 C	0	1600	0
Cream	¾ C	4	680	237
Corn sirup	2 T	0	92	0
Vanilla	1 t	0	0	0
Total		14	2644	327
Chocolate of cream				
Chocolate	1 t	0	4	0
Sugar	1 t	0	20	0
Pastry cream	½ C	1	228	23
Water to fill cup		0	0	0
1 cup or 8 oz		1	252	23
Chocolate of Milk				
Chocolate	1 t	0	4	0
Sugar	1 t	0	20	0
Milk	1 C	8	170	310
1 cup or 8 oz		8	194	310
Cookies				
Butter	½ C	1	877	15
Sugar	⅓ C	0	240	0
Egg	1	6	78	177
Flour	¾ C	11	353	152
Vanilla	½ t	0	0	0
20 cookies		18	1470	344
1 cookie		1	73	17
Soufflé, lemon				
Egg yolk	1	6	78	177
Egg white	1			
Sugar	2 T	0	120	0
Lemon juice		0	0	0
		6	198	177
Pie crust				
Flour	1 C	14	453	198
Lard	3 T	0	405	0
Water		0	0	0
Total		14	858	198
Pie, apple				
Apples	4	0	240	112
Sugar	1 C	0	800	0
Butter	1 T	0	108	2
Lemon juice	1 T	0	4	0
Cinnamon		0	0	0
		0	1152	114
Plus crust		14	858	198
Total		14	2010	312
⅙ pie		2	370	52

FOOD	APPROXIMATE AMOUNT	PROTEIN	CALORIES
		gm	
Squash pie			
Pastry cream	2 T	1	116
Water	3 T	0	0
Sugar	5 T	0	300
Eggs	2	12	156
Squash	1 C	4	64
		17	636
Plus crust		14	858
Total		31	1494
⅙ pie		5	249
Cottage-cheese pie			
Cottage cheese	1 C	36	176
Sugar	⅔ C	0	533
Milk	½ C	4	85
Egg yolks, beaten	2	6	132
Fat, melted	1 T	0	108
Vanilla or lemon juice or nutmeg		0	0
		46	1034
Crust		14	858
Meringue			
Egg white	2	6	24
Sugar	2 T	0	120
Vanilla		0	0
Total pie		66	2036
⅙ pie		11	339

Mix the ingredients in the order given. Bake the pie in one crust. Cool it slightly and cover meringue. Brown in a slow oven.

FOOD	APPROXIMATE AMOUNT	PROTEIN	CALORIES
Pudding, cornstarch			
Pastry cream	¼ C	1	226
Water	¾ C		
Cornstarch	1 T	0	36
Sugar	4 t	0	80
Vanilla	¼ t	0	0
8-oz cup		1	332
Pudding, cornstarch			
Milk	1 C	8	170
Cornstarch	1 T	0	36
Sugar	3 t	0	60
Vanilla	¼ t	0	0
8-oz cup		8	266
Pudding, cornstarch			
Raspberry juice	1 C	0	88
Sugar	3 t	0	60
Cornstarch	1 T	0	36
Lemon juice	1 t	0	0
8-oz cup		0	184
Pudding, cornstarch			
Brown sugar	½ C	0	400
Cornstarch	1 T	0	36
Cream, 40%	¼ C	1	226
Water	1 C	0	0
Butter, salt-free	1 T	0	108
Vanilla		0	0
		1	770

FOOD	APPROXIMATE AMOUNT	PROTEIN	CALORIES	SALT
		gm		mgm
Pudding, custard				
Milk	⅔ C	5	106	203
Egg	1	6	78	177
Sugar	1 t	0	20	0
Flavoring to taste		0	0	0
8-oz cup		11	204	380
Pudding, rice				
Rice, cooked	1 C	3	140	24
Sugar	1 T or 3 t	0	60	0
Cream, 40%	¼ C	1	226	23
Water as necessary		0	0	0
		4	426	47
Mix ingredients together and bake as a custard.				
Pudding, tapioca				
Tapioca	3 T	0	156	12
Grape juice	2 C	0	368	64
Sugar	½ C	0	400	0
Lemon juice		0	0	0
2 servings		0	924	76
1 serving		0	462	38
Any fruit juices may be used.				
Pudding, tapioca				
Tapioca	1 T	0	52	4
Milk	1 C	8	170	310
Egg	1	6	78	177
Sugar	2 T	0	80	0
Flavoring		0	0	0
2 servings		14	380	491
1 serving		7	190	245
Pudding, gelatin				
Gelatin	2 t	6	24	0
Cold water	¼ C	0	0	0
Boiling water	1 C	0	0	0
Sugar	⅓ C	0	267	0
Grape juice	½ C	0	92	16
Lemon juice		0	0	0
2 servings		6	383	16
1 serving		3	191	8
Pudding, gelatin				
Gelatin	2 t	6	24	0
Cold water	1 T	0	0	0
Strong coffee	2 C	0	0	0
Sugar	2 T or 6 t	0	120	0
Cream, 40%	½ C	2	452	46
2 servings		8	476	46
1 serving		4	238	23
Soup, cream				
Cream, 40%	¼ C	1	226	23
Purée vegetable	2 T	1	12	12
Water to fill cup		0	0	0
		2	238	35

Use 2 T any vegetable purée, ¼ C cream, and enough water to make a serving. This type of soup may be seasoned with a few drops of onion juice or a little chopped parsley or a few grains of cayenne pepper.

FOOD	APPROXIMATE AMOUNT	PROTEIN	CALORIES	SALT
		gm		mgm
Mayonnaise				
Egg yolk	1	3	66	28
Oil	1 C	0	2160	0
Vinegar	3 T	0	0	0
		3	2226	28

Add part of vinegar to yolk of egg and flavoring (sugar, dry mustard, or paprika) if desired. Beat with egg beater and add oil slowly, beating all the time.

Cottage cheese				
Milk	1 qt			
Rennet tablet or Junket	2			

[illegible]

Cottage cheese (removal of salt from commercial brands)

Tie cottage cheese in cheesecloth and wash thoroughly by fastening to water tap until the water comes away clear, which will be about 15 to 20 min Knead frequently Then place cheesecloth with cottage cheese in a large container of water and let remain overnight. Remove from water and drain.

Dry skim milk				
Milk powder	¼ C	8	80	310
Water	1 C	0	0	0

[illegible]

Peanut butter

2 C nuts to 1 T oil

[illegible]

Cottage-cheese balls				
Cottage cheese	2 C	72	352	1168
Mashed potatoes	2 C	8	240	152
Egg	1	6	78	177
Bread crumb	½ C	4	112	76
White sauce				
Milk	½ C	4	85	155
Flour	2 T	2	56	24
Fat	1 T	0	135	0
Seasoning (sage, thyme, parsley, pepper, onion)		0	0	0
8 balls		96	1058	1752
1 ball		12	132	219

Make white sauce Gradually beat cottage cheese into it. Add mashed potatoes, season, make into soft balls, roll in bread crumbs, then in beaten egg, then in bread crumbs again. Fry in kettle of deep fat until golden brown.

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